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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1931

ORIGINAL ARTICLES.

INTRAVENOUS VACCINATION WITH STREPTOCOCCI IN RHEUMATIC FEVER.*

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The working hypothesis upon which intravenous vaccination for the treatment of rheumatic fever and the prevention of relapses is based may be stated as follows: Assuming that one of the elements in the pathogenesis of the disease is a condition of hypersensitiveness to streptococci, then by diminishing or eliminating that hypersensitive state by intravenous injection with suitable antigens one might expect a corresponding diminution in the symptoms of the disease.

More in detail, one might postulate that hypersensitiveness as a precursor of an acute attack had been brought to a certain level by long-standing or repeated low-grade focal infection in which streptococci of various types had played a leading rôle. Then an acute infection, for example, tonsillitis or sinusitis, acting in or on these somewhat hypersensitive tissues, tends to increase the condition still further, so that either whole bacteria or their disintegration

* Read before the Association of American Physicians, Atlantic City, May 7, 1930.

products in exceedingly small amounts act as powerful irritants. These irritants appear to attack particularly those mesenchymal tissues most subject to physiologic trauma; hence, lesions commonly occur in such constantly moving structures as joints, tendons, heart and bloodvessels. Admitting hypersensitiveness to be only one of several causative elements of the disease, it still seems logical to assume that could this condition be diminished and a state of immune hyposensitiveness brought about, then less injury would result from superinduced infection.

This general working hypothesis has been evolved in part from a study of patients,[1,2,3] in part from the literature,[4,5,6] but chiefly by analogy from investigations of the reactions of animals to experimental infection with the streptococci under a variety of conditions.[7,8,9,10] It has been determined that the reactive state of the animals is conditioned largely by the mode of inoculation: When into the tissues,[8] in other words, by production of focal infection, the resulting state is one of hypersensitiveness, and subsequent implantation into the tissues of minute doses of relatively avirulent microörganisms results in extensive injury and exudation, followed by proliferation and repair, that is, the response is one of "hyperergic inflammation." When, on the other hand,[9] the preliminary inoculation has been by the intravenous route subsequent infection of the tissues is better tolerated, and the response to suitable doses is a minimum of injury, little, if any, exudation and only moderate proliferation. In other words, the immune hyposensitive animal responds to infection with a minimal disturbance to the local or general body economy. In passing, it may be emphasized that extreme hypersensitiveness has been attained by repeated small inocula: doses too minute to cause visible lesions in normal animals; and that chronic minimal infections seem to exert a more potent sensitizing influence than do acute massive infections.[10] Moreover, highly sensitized animals give hyperergic inflammatory responses not only to the homologous strain used for sensitization, but also to immunologically and culturally unrelated strains of streptococci.

But still more important from the viewpoint of the second part of our introductory hypothesis is the demonstration that most hypersensitive animals can be rendered immunely hyposensitive by suitable intravenous vaccination.[3,11] The most effective desensitization or immune hyposensitization has been attained by intravenous immunization with strains homologous to the one with which the animals have been sensitized; more distantly related strains, even though suitable for detection of a hyperergic state, may fail to desensitize so completely and effectively when injected intravenously. Furthermore, it has been more difficult to desensitize animals in which constantly renewed focal infections were induced than those from which sensitizing foci had been previously removed.

For the above-mentioned reasons the selection of a suitable

antigen for immunizing patients offered certain difficulties. If one attributes an etiologic rôle to the streptococci obtained by blood culture from patients with rheumatic fever, then numerous cultural and immunologic unrelated strains must be held responsible for the symptom complex.[5,12,13] On the other hand, it is conceivable that all of them possess some common constituent or elaborate similar toxic substances which act as the noxious agents. But tonsillitis, probably caused by hemolytic streptococci, is the precursor of many attacks of rheumatic fever; often the angina accompanying acute polyarthritis or carditis is associated with a fairly heavy hemolytic streptococcus infection of the tonsils or pharynx. We have observed onset of recurrences to be preceded by otitis media with an exudate yielding a pure culture of hemolytic streptococci. Many of our patients have harbored almost pure cultures of hemolytic streptococci in their tonsils for months following an acute attack of polyarthritis, and at times the operative removal of such tonsils has marked the turning point toward recovery. Moreover, scarlet fever, acknowledged to be of hemolytic streptococcus origin, is not infrequently followed by a rheumatic symptom complex; and Siegmund[14] has lately described microscopic granulomata closely resembling rheumatic lesions in the cardiovascular system or subjects dying several weeks after the onset of scarlet fever. It has, furthermore, been determined that many patients with rheumatic fever are very sensitive to intracutaneous and intravenous injections of hemolytic streptococci, either in the form of heat-killed vaccines or of nucleoproteins. For these reasons it seems that hemolytic streptococci may play a more important rôle in the production of rheumatic fever than has heretofore been considered probable; hence the immunizing substance first selected was of hemolytic streptococcal origin. Other types were added later.

The strain Q33, first used for the preparation of a vaccine, was isolated from the tonsillar exudate of a patient who had suffered for months from severe polyarthritis and carditis with congestive failure, showing little tendency toward recovery. His reaction to intracutaneous injection of 500,000 heat-killed organisms was marked, compared with very slight lesions in normal individuals. Following intravenous injections of vaccine consisting of 1,000,000 and 10,000,000 streptococci on two successive days he had fever about 102° F. for three days, precordial pain and some ectopic beats; these symptoms quickly disappeared following antirheumatic medication, and this acute fever was followed shortly by improvement going on to recovery, which persisted for three years.* Another patient with persistent polyarthritis showed the first distinct signs of improvement following intravenous injection of a dose of 10,000,000 of the same vaccine and recovered completely after three more

* Recently this patient developed auricular fibrillation following a strenuous bacchanalian and terpsichorean celebration; but without fever or other signs of renewed rheumatic infection.

doses. In a third patient a similar quantity of vaccine intravenously induced high fever for several days which eventually required large doses of neocinchophen for its control, but this episode was followed by a decided amelioration of his condition.

As the improvement in all of these cases might have been attributed to nonspecific protein shock therapy, the result of high fever, it became desirable to determine whether similar alterations in the course of the disease might not be more slowly induced by progressive immunization, beginning with small doses and gradually increasing them until relatively large amounts could be given without inciting severe reactions. It was found that patients giving the most marked reactions to intracutaneous injections of vaccines or nucleoproteins also reacted most violently to intravenous injections; hence, these cutaneous reactions served at first as a rough guide to size of initial dose. But recently it has been more convenient to start with small initial doses, and increase them gradually to larger amounts.

The postvaccinal reactions deserve special attention. As a rule, they have been more marked in the early stages of the disease, although in an occasional patient with long-standing infection they have been very intense. The maximal fever has usually occurred within twelve to thirty-six hours following the vaccination, but in an occasional patient it has been delayed two or three days. In patients not under the influence of antirheumatic drugs reactions have occasionally been somewhat alarming in their severity, and resembled acute rheumatic relapses, by evoking renewed signs of arthritis. Several patients with rheumatic erythema circinata have had an astonishing increase of this peculiar dermatosis the day following vaccination. Signs of cardiac focal reaction have consisted of palpitation, ectopic beats, mild tachycardia and transitory gallop rhythm. Such postvaccinal responses have been much less severe in patients fully under the influence of antirheumatic drugs, and when encountered in patients not receiving such drugs they have been quickly terminated by intense drug therapy. In this respect, again, they have resembled rheumatic relapses. Patients who have developed a tolerance to a certain dose of vaccine have shown renewed sensitivity to the same dose if they have suffered a rheumatic relapse or become the subjects of acute upper respiratory infection. During catamenia women have responded uncomfortably to doses previously well tolerated. In several patients reactions to the same sized dose were distinctly less after the removal of chronically infected tonsils.

Because of these reactions we feel that patients with marked active rheumatic carditis accompanied by signs of congestive failure should, if they are treated with vaccines at all, be very cautiously vaccinated. In such individuals the balance is so easily disturbed that, being already unfavorable, the resistance may be still further and irremedially depressed if too severe reactions occur. On the

other hand, in patients who have recovered from the active infection, but in whom vaccination is used in an attempt to prevent further relapses, unpleasant postvaccinal reactions have been only rarely encountered.

In patients in the subacute or chronic stage of the disease, with increasing tolerance to larger doses of vaccines there has been a corresponding decrease in signs of activity of the rheumatic process.

For example, a boy, R. D., aged fourteen years, suffering for many months from active carditis, mild but persistent polyarthritis and fever which could be controlled only by full doses of drugs, and which relapsed with each drug withdrawal, was slowly immunized, beginning with a dose of vaccine containing 2,500,000 microörganisms, and increasing progressively to 10,000,000. Early the treatments were followed by marked focal reactions; but later when the larger doses could be tolerated, even though the patient was not under the influence of drugs, he showed satisfactory clinical improvement, so that tonsillectomy could be safely performed. In spite of permanent valvular damage he has resumed and continued a very active school life. (See Fig. 1.)

Another patient, J. G., a woman, aged twenty-three years, had a severe extensive polyarthritis, not completely relieved by large doses of neocinchophen. While under the influence of this drug she showed focal reactions at the beginning with doses of vaccines containing 500,000 organisms, but later, as tolerance to vaccines increased, there was decreasing arthritis which finally disappeared. (See Fig. 2.)

From the results in such cases it was felt that a slow immunization was accountable for the decrease in symptoms, for the postvaccinal reactions were not severe enough to permit one to attribute the changed reaction to febrile nonspecific shock. We recognize that in most cases of rheumatic fever the tendency is toward recovery of varying degrees of permanence. Such recovery is due either to removal of the noxious agent or to a gradually built-up immunity. If our assumptions are correct, by intravenous vaccination we are merely accelerating the immunizing process, and at times inducing a state of resistance in a patient who otherwise seems incapable of spontaneously developing it. Several patients were encountered with persistent low-grade fever in whom a normal temperature followed the institution of vaccination. But in others the vaccination seemed to have no comparable influence. In several of these recovery occurred weeks or months after discontinuing the treatment; in others evidence of low-grade infection still persists. Incidentally it may be mentioned that most patients refractory to ordinary treatment plus vaccination and tonsillectomy have had persistent signs of infection of the paranasal sinuses.

Three forms of vaccine have been employed: (1) Whole heat-killed hemolytic streptococci; (2) nucleoprotein from hemolytic streptococci; (3) a mixture of pulverized streptococci. The whole

vaccine was prepared from the centrifugate of twenty-four-hour broth cultures, resuspended in normal salt solution, heated at 56° C. for one to two hours and then tested for sterility. This was diluted to the required strength with normal salt solution containing 0.5 per cent phenol. The nucleoprotein was prepared by precipitat-

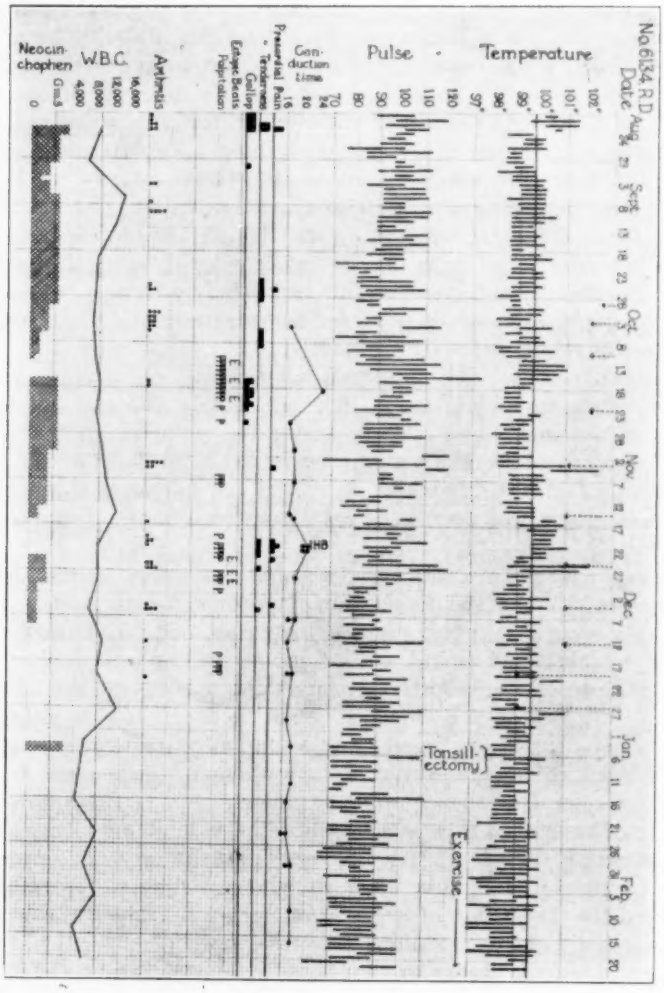

FIG. 1.—Course of patient, R. D., during intravenous immunization with hemolytic streptococcus vaccine. Each day is represented by a vertical column. Ranges of temperature and pulse for a day are indicated by respective columns. Under conduction-time, *I H B* indicates incomplete heart block. *E* indicates ectopic beats on day recorded. *P* indicates palpitation on day recorded. Under arthritis, each block represents a joint involved on the day recorded. Absence of blocks indicates no clinical evidence of arthritis. Dose of vaccine ranging from 2,500,000 to 10,000,000 indicated by length of arrows.

ing with weak acetic acid from a weak sodium hydrate solution of hemolytic streptococci.[15] The mixture of pulverized streptococci, so-called "Triple BE," was made as follows: A broth culture centrifugate was frozen and dried *in vacuo*, then ground in a ball

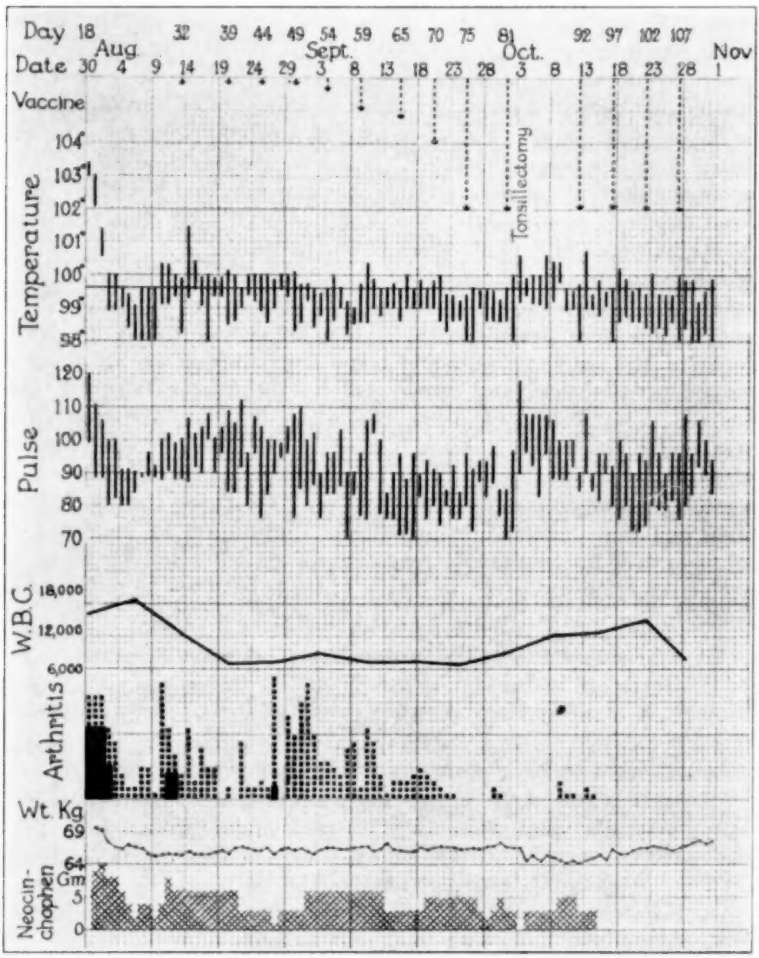

FIG. 2.—Course of patient, J. G., during intravenous immunization with vaccine prepared from hemolytic streptococcus cultured from patient's own tonsil. Under arthritis, the number of joints involved on a given day is indicated by the height of the respective column: Solid, shows severe arthritis; lighter block, mild arthritis, *e. g.*, first day, 11 severely involved joints and 4 mildly involved. Dose of vaccine ranging from 500,000 to 10,000,000 indicated by length of arrows.

mill for from two to three weeks, until only an amorphous powder remained which showed no Gram-positive forms in films and yielded no growth in suitable media. This was suspended in phenolized normal saline, and cultured repeatedly to insure sterility. Equal

parts, by dry weight, of the suspended powder from three different streptococci—a hemolytic, a green and an indifferent form—were combined, and the dose figured in fractions of a milligram of the combined dry powder. The dose of the whole vaccine has ranged from 50,000 to 10,000,000 microörganisms, that of the nucleoprotein from 0.001 mg. to 0.5 or 1 mg. of the dried substance and that of the triple streptococcus BE from 0.0001 mg. to 0.05 or 0.1 mg. of the combined powders. In patients having active infection the course has started with smaller doses; in those in subacute or chronic stages, with somewhat larger; and when used as a prophylactic measure the initial dose has been still larger. Each succeeding dose has usually been double that preceding unless the postvaccinal reactions have been marked; in such cases the dose has been held constant until reactions were only slight, when it was increased.

All three forms when injected intravenously into hypersensitive rabbits have been shown to change the reactivity of such animals to one of immune hyposensitivity. There are certain theoretic advantages of the different antigens respectively which are at present under investigation, and hence will not be here extensively discussed. The results of using the whole vaccine prepared from strain Q33 at the New York Nursery and Child's Hospital in an attempt to prevent relapses in rheumatic children is reported in another communication. Briefly, it may be stated that such vaccinations were followed by a distinct diminution in incidence of relapses.[16] The results of treatment of patients having signs of active infection are given in Table I; these patients have been followed for periods of from a half to two and a half years.

Summary of Results in Intravenously Immunized Patients.

	Immunization and recovery parallel.		No distinct effect.	Total.
	No relapse.	Relapse.		
Hemolytic streptococcus vaccine	11*[4]	2	2	19
Hemolytic streptococcus nucleoprotein	8*[3]	2	3	16
Triple streptococcus ground emulsion	3*[1]	6	2	12
Vaccine followed by nucleoprotein	..	..	1	1
Nucleoprotein followed by triple streptococcus emulsion	..	..	2	2
Vaccine followed by triple streptococcus emulsion	1	..	..	1
Total	23*[8]	10	10	51

* Not seen since discharge.

It will be seen that in about four-fifths of the patients increasing tolerance to the vaccine was accompanied by improvement; but that improvement or recovery persisted longer in a higher proportion of those receiving whole vaccine. The different groups are too small for significant statistical comparison; but from a theoretical standpoint one might expect a more solid immunity from intravenous vaccination with whole microörganisms than with partial antigens.

On the other hand, focal reactions might be more extensive from introduction of the former than the latter. As already mentioned, these are subjects for further investigation.

Discussion. We may now ask: To what extent has the hypothesis of hypersensitiveness to streptococci as a factor in the pathogenesis of rheumatic fever been borne out by these investigation?

The fact that, in patients with active disease, both febrile and focal reactions following vaccination have many resemblances to true rheumatic relapses and that these can be either prevented or terminated by antirheumatic drugs, is highly suggestive. But similar focal reactions have been described following the subcutaneous injection of tuberculin into rheumatic patients.[17] Selter[18] has demonstrated, however, that an animal or man sensitive to two different bacteria may show cross-focal reactions when either antigen is used for testing. We know, however, of no demonstration or apparent interruption of the course of rheumatic fever following the institution of prolonged tuberculin therapy.

The observation that the majority of patients in active stages of the disease react to one strain of hemolytic streptococci does not indicate that they have necessarily been sensitized to that strain, for an animal made highly sensitive with one streptococcus will show hyperergic reactions with distantly related streptococci. On the other hand, the diminution in rheumatic symptoms running parallel with increasing tolerance to a given strain is more suggestive of the hypersensitivity to that strain and the symptoms of the disease having a causal relationship; for, as previously mentioned, the most effective antigen for immunizing desensitization of hypersensitive rabbits is a strain homologous with, or one closely related to, the strain used for sensitization. If this evidence is applicable to the interpretation of our clinical results it would appear that the sensitization responsible in part for the pathogenesis of rheumatic fever was induced by strains closely related to hemolytic streptococci.

The failure, however, of a fair proportion of the patients to react favorably to immunization with a single strain suggests that this immunizing strain is too far removed antigenically from the sensitizing strain to be an effective therapeutic agent; or, in other words, that the sensitization in different patients is due to far distantly related microörganisms. The problem then resolves itself into a more accurate determination of the strain or strains responsible for the maintenance of the hypersensitive state. If this information is obtainable we shall probably be in a more favorable position for attaining effective immunization.*

* The etiologic and immuniologic significance of the recent finding of a high percentage of positive blood cultures by various workers, such as Clawson,[9] Cecil, Nicholls and Stainsby,[13] and others has not as yet been finally determined. If it should eventually be determined that a few strains played a definite etiologic rôle in the disease, then the production of a high degree of active immunity against them would probably be an effective therapeutic procedure.

Another alternative, which we are at present pursuing, is to test the effect of increasing the number of strains in the immunizing mixture. If it could eventually be demonstrated that the majority of patients reacted to a polyvalent antigen which included representative strains of a few types the problem would be considerably simplified. But, so far as our present experience with immunization indicates, if the symptom complex known as rheumatic fever is due to streptococci a number of different strains or types are responsible, and this, moreover, is in conformity with the hypothesis as evolved from the results of cultures of streptococci isolated from the blood and tissues of patients with the disease, and also from the results of testing patient's cutaneous reactions with different types.

Finally, we are fully aware of the pitfalls in therapeutic investigations of this type. The great variability in the course of rheumatic fever in different individuals renders difficult the judgment of results in relatively few cases. The favorable response of many rheumatic fever patients to different forms of nonspecific protein shock therapy suggests that any beneficial effect obtained by us may have been due to this form of sudden stimulation of resistance. But our efforts have been to avoid high fever and the accompanying shock, and good therapeutic responses have followed slow immunization in the absence of these reactions.

Another criticism is the lack of control cases in which other bacterial antigens have been employed. Before resorting to such controls we felt it necessary to test an antigen which probably had a close relationship to the disease. Moreover, animal experiments have demonstrated the necessity of keeping the material used for immunizing desensitization antigenically close to the sensitizing microörganism.

Still another proper inquiry is the advantage of intravenous over subcutaneous vaccination. From the experience with animals one may state that injection of streptococcal vaccines into the tissues usually tends to sensitize, while intravenous injections tend to diminish the overreactivity of hypersensitive tissue. To combat a condition of hypersensitiveness, therefore, the logical method would be intravenous inoculation under proper precautions. In addition, the local reactions about the site of subcutaneous vaccination with streptococci are often so intense that patients are unwilling to have them repeated. Intravenous injections, on the other hand, are free from local reactions, and most patients are willing to continue them for a full course; hence, from both a theoretical and practical viewpoint the intravenous route is the one of choice.

We do not feel that the results up to the present time have a final character, but must be considered as a first approximation. They are sufficiently favorable to warrant continuation and elaboration of the method. It is especially applicable to two classes of patients: (1) Those with a continuing low-grade infection; (2) those temporarily free from symptoms but in whom relapses may be reason-

ably expected.[16] If in these two classes, by this means of immunization the natural resistance of the tissues can be so enhanced that subsequent infection is met and tolerated with only a minimum of injury, the method will have been justified.

Subsequent to the preparation of this communication appeared the report of Clawson and Fahr (*Proc. Soc. Exp. Biol. and Med.*, 1930, **27**, 964) on intravenous vaccination of 8 rheumatic fever patients with heat-killed green streptococci. Although high agglutinin titers in the blood serum resulted, no clinical data were reported.

Also, in the recent report of the work of Small (*J. Lab. and Clin. Med.*, 1930, **15**, 1093) with intravenous injections of Streptococcus cardioarthritidis soluble antigen, the doses are so different from the ones above reported that the mechanism can hardly be compared.

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THE ETIOLOGY OF RHEUMATOID ARTHRITIS.*

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Rheumatoid arthritis is one of the great mysteries of medicine. Though considerable light has been thrown on this disease during the last few years, much work and study by many investigators have failed to disclose the true nature of the malady, and in the new edition of the *Encyclopedia Britannica*, it is still described as a disease of unknown etiology.

We have chosen to call the disease rheumatoid arthritis because this title is the most noncommittal of its numerous synonyms. The term "chronic infectious arthritis" is now very popular, but in view of the fact that some investigators still question the infectious nature of the disease, rheumatoid arthritis would seem to be preferable.

The present status of rheumatoid arthritis is not unlike that which existed with respect to tuberculosis before Robert Koch isolated the tubercle bacillus. Prior to this discovery, many theories concerning the etiology of pulmonary tuberculosis had been formulated. Medical textbooks and treatises on tuberculosis written before Koch's historic announcement contain long dissertations on the importance of heredity, bad air, improper food, morbid conditions of the blood, bronchial catarrh, improper innervation of the lungs and so forth, as causes of pulmonary tuberculosis. Then came Pasteur, the realization that tuberculosis was an infection and, finally, the isolation of the tubercle bacillus. It was realized at once that the causes which had been previously stressed were not exciting causes, but simply predisposing factors in the etiology of the disease. A situation quite similar to this had existed with regard to rheumatoid arthritis. Various etiologic theories have been advanced, such as heredity, exposure to cold and wet, the neurotrophic theory of Weir Mitchell, disturbed carbohydrate metabolism and inadequate circulation in the joints (both emphasized by Pemberton[1]), the intestinal putrefaction theory, supported by Arbuthnot Lane and others, and, finally, infection and the focal infection theory, which now has many supporters.

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If the infectious nature of rheumatoid arthritis is successfully established, and if a specific microörganism can be isolated with any degree of regularity from the lesions of this disease, it will at once be evident that the above-mentioned etiologic factors are merely predisposing causes, not the actual causes of the disease.

After several years of investigation into the etiology of rheumatoid arthritis, the writers have come to believe that this particular joint syndrome is a chronic infection caused in the great majority of cases by a specific type of streptococcus. Doubtless there are comparatively few who would be willing to accept this definition without some qualifications, and perhaps further investigations may eventually prove that this position is erroneous. At present, however, the evidence in support of the streptococcal theory is very strong. We wish briefly to consider this evidence as it bears on the following questions:

1. Is rheumatoid arthritis an infection?
2. If rheumatoid arthritis is an infection, is it a streptococcal infection?
3. If it is a streptococcal infection, how do the streptococci gain access to the joints?

1. What evidence is there that rheumatoid arthritis is an infectious disease?

(*a*) *Clinical Evidence.* The clinical evidence in support of the infectious theory is considerable. In the first place, patients with rheumatoid arthritis almost invariably give a history of numerous previous infections, such as tonsillitis, sinus trouble, root abscesses about the teeth, sore throats, common colds and genitourinary or pelvic infections. We have been surprised in going over our records to find how many of these rheumatoid patients have had appendicitis or cholecystitis. No doubt it was this obvious prevalence of past and present infections that gave Billings[2] and his coworkers the clue to focal infection as a causative factor in rheumatoid arthritis. Certainly it is exceptional to encounter one of these cases without some focus of infection. In many cases, of course, the focus has been removed by the time the patient comes under observation; unfortunately, it is often removed too late to have much effect on the already well-established infections in the joint; in our experience, however, a rheumatoid patient without a focus of infection, or at least the history of a focus, is rarely encountered.

The clinical course of rheumatoid arthritis is strongly suggestive of a chronic infectious disease. Starting in sometimes with acute symptoms, the patient develops fever, general malaise and sharp pain and swelling in the joints. The joint symptoms are usually migratory and suggestive of rheumatic fever. A slight leukocytosis is often present, and as the disease progresses a secondary anemia is a frequent occurrence. When the onset is gradual the insidious

but progressive swelling of the joints presents the picture of a chronic infection. The patient often loses weight and strength and becomes pale and chronically ill. The joints are swollen and tender and bear considerable outward resemblance to other forms of chronic arthritis known to be caused by bacteria, such as gonococcal, tuberculous and luetic arthritis. The perfect analogue of rheumatoid arthritis is gonococcal arthritis, a well-recognized infection characterized by a primary focus in the genitourinary tract with metastatic infections in the joints. Incidentally it should be noted that gonococcal arthritis occasionally progresses into a condition clinically indistinguishable from advanced rheumatoid arthritis with ankyloses and deformities.

Some of the concomitants of rheumatoid arthritis give every appearance of metastatic infections, particularly iritis and the subcutaneous fibrous nodules. It is difficult to explain either of these inflammatory conditions on any other basis than the infectious one.

(*b*) *Pathologic Evidence.* Any student of arthritis who will stand at the elbow of an orthopedic surgeon during an operation on a rheumatic joint cannot fail to realize that the lesions which characterize rheumatoid arthritis are essentially *inflammatory* lesions, similar in all respects to those observed in other well-known infections of the joint. The swelling of the soft tissues, the thickened capsule, the cloudy synovial fluid, the red, swollen, edematous synovial membrane and the ulcerated cartilage all spell infection to the eye of a pathologist.

Microscopically the histologic changes are those of a chronic infectious process. In a section taken through the synovial membrane the surface is often found covered with a thin layer of necrotic material densely infiltrated with leukocytes, beneath which there is vascular granulation tissue rich in fibroblasts, monocytes and leukocytes of various kinds. The subcutaneous nodules are also composed of definitely inflammatory tissue.

(*c*) *Bacteriologic Evidence.* This, of course, is the most important link in the chain. In order to establish finally the infectious nature of any disease, the same microörganism must be isolated with a fair degree of regularity from the lesions of that disease. A considerable amount of research has been directed toward the bacteriology of rheumatoid arthritis, but little of it has thrown much light on the real nature of the condition. The frequent presence of streptococci in the various foci of infection which are associated with rheumatoid arthritis has naturally focused the interest of bacteriologists on this organism. Time does not permit a review of the literature on the subject, but suffice it to say that though a number of investigators have succeeded in isolating streptococci from both the blood and joints of patients with rheumatoid arthritis, the percentage of positive results has been too small to be convincing. Perhaps the one exception to this statement is

the report of Forkner, Shands and Poston,[3] who took cultures from the joints in 63 cases of chronic infectious arthritis and recovered a Streptococcus viridans in 11 (17 per cent) of the cases. Crowe,[4] believes that rheumatoid arthritis is caused by a staphylococcus, but the evidence which he presents is far from convincing.

This leads up to the second question presented in the introduction to this discussion:

2. If rheumatoid arthritis is an infectious disease is it a streptococcal infection?

During the past three years an intensive bacteriologic study of rheumatoid arthritis has been conducted on the Second Medical Division of Bellevue Hospital and in the Cornell Clinic.[5] The cases included in this investigation have been carefully selected from a large group of miscellaneous joint conditions, inflammatory, traumatic, degenerative, and so forth. We have felt very strongly from the outset that rheumatoid arthritis is a definite clinical syndrome to be sharply differentiated from various other articular disturbances and from the degenerative arthropathies which occur after middle age. The patients selected, however, were in various stages of the disease. Some were in the incipient stage with migratory pains and only slight swelling of the joints. Others were quite advanced, with ankyloses and deformities. A great majority represented what might be called the mean between these two extremes. The two almost universal symptoms were pain and swelling in several joints.

A large number of patients with this disease have been subjected to blood cultures and a considerable number to both blood cultures and joint cultures. In a number of instances repeated cultures have been made on the same patient. The technique, modified from that of Clawson,[6] may be summarized briefly as follows:

For blood cultures 20 cc. of blood is taken from the arm, placed in two sterile culture tubes and allowed to clot. The tubes are centrifuged, the serum withdrawn, the clot broken up and transferred to bottles of beef heart infusion broth with a pH of 7.6. The bottles are placed in the incubator at 37° C. Every seven days subcultures are made from the original flasks on blood-agar plates and in blood-broth tubes. All cultures and transfers are made in a sterile chamber. Joint cultures are made in blood broth by adding a few drops of synovial fluid to each tube of broth. These cultures, like the blood cultures, are incubated for several weeks and subcultured from time to time.

Altogether 154 cases of rheumatoid arthritis have been subjected to blood cultures by this method. The results are shown in Table I. Of the 154 patients cultured, 96 (62.3 per cent) yielded a short-chained streptococcus. In several patients a streptococcus was obtained in two or even three successive cultures. In other patients one blood culture was positive, while a second was sterile, or *vice versa*. In 3 cases a diphtheroid bacillus was recovered from the

flasks. This organism is apparently not a contamination, but is actually present in the circulating blood. It appears, however, to be a harmless saprophyte. Occasionally a Staphylococcus albus or some spore-bearing bacillus has been recovered from the blood cultures, but these organisms have been looked upon as contaminations.

TABLE I.—BLOOD CULTURES.

Condition.	Cases.	Positive.	Per cent.
Rheumatoid arthritis	154	96	62.3
Controls	104	4	3.8

Control Cultures. As a control on these findings, 104 indivuals, either normal or suffering from some condition other than rheumatoid arthritis, were subjected to blood cultures, the technique being similar in all respects to that used on patients with rheumatoid arthritis. (Table II.) Of these controls 20 were normal healthy individuals with no joint symptoms and no obvious foci of infection. The remainder of the control group were patients suffering from some disease. Of these 23 were middle-aged patients, who presented a typical picture of degenerative arthritis with hypertrophic changes in the bones. The blood cultures on all this group were sterile. The remaining 61 controls were patients suffering from various diseases, including infections of various kinds. Of these 61 patients 4 showed Streptococcus viridans in their blood cultures. The 4 positive controls presented certain features in common, as is evident from the following protocols:

TABLE II.—CLASSIFICATION OF CONTROL BLOOD CULTURES.

Condition.	Cases.	Positive.
Normal individuals	20	0
Degenerative arthritis	23	0
Miscellaneous	61	4

Protocols. H. T., male, aged sixty years. Onset two weeks before admission to Presbyterian Hospital with fever, cough and expectoration. Diagnosis: Pansinusitis, acute and chronic bronchitis and cardiac insufficiency. Blood culture yielded Streptococcus viridans. Temperature at time of blood culture was 102° F.

I. W., male, aged twenty-seven years. Admitted to the Presbyterian Hospital with five months history of nervousness and weakness. Basal metabolism, +52. Tonsils large, red and spongy. Diagnosis: Exophthalmic goiter and chronic tonsillitis. Blood cultures showed short-chained streptococci in the sediment, but the organism was never isolated.

C. H., male, aged thirty-four years. Chronic sinusitis. Weekly irrigations of antrum for several months. Blood culture yielded a Streptococcus viridans. Several weeks following the patient developed muscular pains and had to go South for a vacation.

B-284, male, aged fifty-three years. Onset six hours before admission to Bellevue Hospital with muscular pain in back and legs. General malaise and high fever. Physical examination negative except for a reddened

pharynx. Diagnosis: "Fever of unknown origin." Blood culture taken on day of admission (temperature, 104.6° F.) yielded a Streptococcus viridans.

It is significant that of the 4 controls with positive blood cultures 3 had active foci of infection of the type usually associated with arthritis, while the fourth showed a red throat and high fever.

Joint Cultures. In 49 cases of rheumatoid arthritis cultures were made from one of the affected joints. (Table III.) In 33 cases (67.3 per cent) a short-chained streptococcus was recovered from the joint cultures. In 48 cases that were subjected to both blood cultures and joint culture 37 (77 per cent) showed a streptococcus in either the blood or the affected joint. In 2 cases cultures from the knee joint yielded a diphtheroid bacillus.

TABLE III.—JOINT CULTURES.

Condition.	Cases.	Positive.	Per cent.
Rheumatoid arthritis	49	33	67.3
Controls	18	0	0

Control joint cultures were made on 18 patients who were suffering from some condition other than rheumatoid arthritis. In Table IV the joint culture controls are listed according to disease. The joint cultures from these 18 controls all remained sterile.

TABLE IV.—CLASSIFICATION OF CONTROL JOINT CULTURES.

Condition.	Cases.	Positive.
Degenerative arthritis	5	0
Gout	1	0
Intermittent hydrops	2	0
Synovitis	9	0
Osteitis fibrosa cystica	1	0

Cultural Characteristics of Streptococci. On culture media the streptococci which have been recovered from the blood and joints of patients with rheumatoid arthritis present a strikingly similar appearance. They all have one feature in common, that is, very slow growth in the original blood-culture flasks. The average time of appearance of these streptococci in the original cultures is approximately fifteen days. Subcultures, on the other hand, grow rapidly on the usual laboratory media. The colony of a typical strain on blood-agar plates presents the appearance of a Streptococcus viridans. On subculture, however, many of these produce some hemolysis both on blood agar and on blood broth. Morphologically the "typical strain" is a small Gram-positive coccus, which on solid media grows in short chains. In liquid media longer chains are formed. In blood broth the streptococcus grows readily with the production of a granular or flocculent sediment with a slight turbidity of the media. In plain broth it produces a considerable amount of sediment and throughout the media a heavy granular growth

which adheres to the sides of the tube. All of the strains have been insoluble in bile.

In 3 patients streptococci recovered from blood cultures resembled the indifferent strains described by Small[7] and Birkhaug.[8]

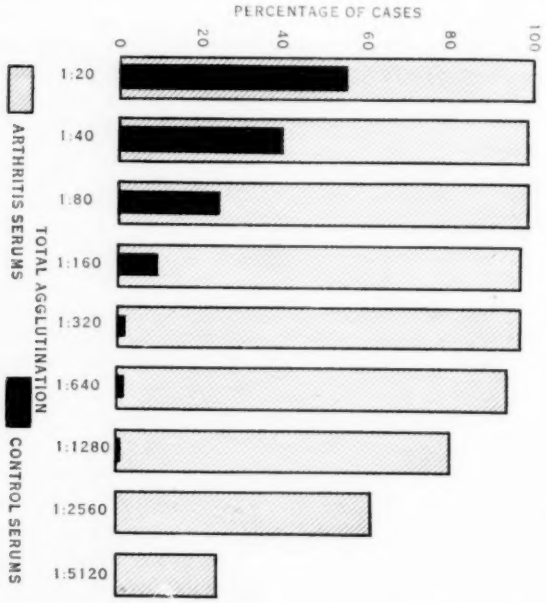
Fermentation Reactions. Forty-three of the streptococcal strains have been tested on sugars. (Table V.) Thirty-six strains fermented dextrose, lactose and salicin, but did not ferment mannite or inulin. Four strains fermented four of the sugars, but had no effect on inulin, and three strains fermented all five sugars.

TABLE V.—FERMENTATION REACTIONS.

Strains.	Dextrose.	Lactose.	Salicin.	Mannite.	Inulin.
36	+	+	+	−	−
4	+	+	+	+	−
3	+	+	+	+	+

TABLE VI.—AGGLUTINATIONS WITH PATIENT'S SERUMS AGAINST TYPICAL STRAINS.

Condition.	0 to 1 : 320.	1 : 640 to 1 : 5120
Rheumatoid arthritis	6	97
Normal controls	50	0
Pathologic controls	102	2



AGGLUTINATIONS WITH PATIENT'S SERUMS AGAINST TYPICAL STRAINS.

Agglutination Reactions. The morphologic and cultural similarity of the streptococci recovered from the blood and joints of patients with rheumatoid arthritis suggested the possibility that they were biologically identical. The serums of patients with rheumatoid

arthritis were, therefore, tested for agglutinins against several "typical strains" of streptococci. To our surprise we found that the serum of practically every patient with well-developed rheumatoid arthritis gave a strongly positive agglutination with the "typical strains" of streptococci. In the average case the agglutination titer ran from 1 to 1280 to 1 to 5120. In early cases the agglutination reactions were not so strong, but even in these patients they usually showed a titer of 1 to 640 or higher. Table VI and chart show the results of agglutination tests on 257 individuals. In a series of 103 cases of rheumatoid arthritis 97 showed an agglutination with the "typical strain" of streptococcus at a dilution of 1 to 640 or higher. In a series of 50 normal controls the serum in every case failed to give a strong agglutination reaction. In 102 pathologic controls only 2 patients gave a positive reading at a dilution of 1 to 640 or higher. It is probably not overestimating the case to say that there is now available an agglutination reaction for rheumatoid arthritis which is quite as specific and reliable for differentiating this condition as is the Widal test for typhoid fever. After recovery from typhoid fever agglutinins gradually disappear from the blood. In a similar way the agglutinins for the streptococcus disappear from the blood of an arthritic patient when recovery takes place. The following 3 cases are good examples:

Protocols. M. P., female, aged twenty-seven years. Pain, stiffness and some swelling of various joints for two years. Two blood cultures yielded each a "typical strain" of streptococcus. Patient's blood agglutinated the "typical strain" at a dilution of 1 to 1280. Following tonsillectomy the symptoms in the joints gradually disappeared. Three weeks after tonsillectomy the agglutination test was positive at only 1 to 320. One year after tonsillectomy the agglutination test was entirely negative.

M. D., female, aged thirty years. Migratory pain and stiffness in various joints of three months' duration. Slight swelling of fingers. Blood culture negative, but patient's serum agglutinated the "typical strain" of streptococcus at a dilution of 1 to 1280. Three weeks after tonsillectomy agglutination was positive at a dilution of only 1 to 40. Three months after tonsillectomy the agglutination test was entirely negative. The joint symptoms cleared up except for occasional twinges in the muscles of the right shoulder. Patient considers herself cured.

S. W., male, aged fifty years, gave a history of three months' pain and stiffness in various joints, affecting chiefly the left shoulder and knuckles of both hands. Physical examination showed crepitation and pain on movement of left shoulder. Tonsils were red, partially buried and infected. Patient's serum agglutinated the typical strain of streptococcus at a dilution of 1 to 2560. Tonsillectomy was done and the patient left at once to spend the summer in Europe. Three months later the patient was much improved, with only slight stiffness remaining in left shoulder. A second agglutination test was performed, and on this occasion the reaction was entirely negative.

The comparatively rapid disappearance of the streptococcal agglutinins as the patient tends to recover speaks strongly for the specific nature of the infection.

Still further evidence of the specificity of these agglutinins was obtained by testing the serums from arthritic patients against other organisms: Pneumococcus Types I, II and III, Bacillus coli, Staphylococcus albus and aureus, strains of Streptococcus hemolyticus and viridans from the normal throat and, finally, Streptococcus scarlatinæ and Streptococcus erysipelatis. It was found that the serums from patients with rheumatoid arthritis agglutinated scarlet fever and erysipelas strains of streptococci in just as high dilutions as they did the arthritic strains; on the other hand, there was practically no agglutination with any of the other bacteria, not even with the streptococci from the healthy throat. All agglutinations were controlled by absorption tests. These findings do not detract in any way from the value of the agglutination reaction in making a differential diagnosis of arthritis, as neither scarlet fever nor erysipelas would ever be confused with arthritis.

Positive agglutination reactions with arthritic streptococci were also obtained with the serum from rabbits immunized against "typical strains" of arthritic streptococci. Table VII shows the results obtained when 46 strains of streptococci were tested against the serums of seven rabbits, each immunized against a "typical strain" of streptococcus. Thirty-seven out of the 46 strains were agglutinated by the immune rabbit serum in dilution of 1 to 1280 or higher. Six strains were agglutinated with low dilutions of serum (1 to 20 to 1 to 80), and only three strains failed to show any agglutination at all with the immune rabbit serums. Furthermore, although each of the seven rabbits had been immunized with a different "typical strain," the reactions of the streptococci with the seven sera were almost identical. A complete protocol of these agglutination reactions with controls will be found in an article published by us elsewhere,[5] which also contains a complete record of absorption tests carried out with "typical strains" of streptococci against typical strain rabbit serum. In the experiments it was found that almost complete absorption of agglutinin took place when "typical strains" of streptococci were added to immune rabbit serum incubated at 37° C. for two hours and allowed to stand in the refrigerator overnight.

TABLE VII.—CROSS-AGGLUTINATION REACTIONS WITH IMMUNE RABBIT SERUMS.

No. of strains.	T.S. immune serums (7).
37 T.S.	1:1280 or over
6	1:20 to 1:80
3	0

The Relation of Streptococci Recovered From the Blood to Streptococci Isolated From the Joints and Other Foci. An interesting phase of this investigation has been the correlation of streptococci isolated from the blood with streptococci cultured from the joints and from various foci of infection. In a number of cases streptococci morphologically, culturally and biologically identical have been

recovered from the blood, the joint and some focus of infection in the same patient. In one case (A-11301) apparently identical strains of streptococci were recovered from the blood, from the joint and from infected tonsils. In another case (A-94403) identical strains were recovered from the blood, from the tonsils and from an erythematous bulla on the skin. And in still another case (R-101) identical strains were recovered from the blood, from the joint and from an apical root abscess about one of the teeth. In each of these instances the identity of the strains recovered was established by the usual morphologic, cultural and biologic tests.

In 48 cases of rheumatoid arthritis cultures have been made both from the blood and from one of the affected joints in the same patient. In 21 cases (43.8 per cent) streptococci were recovered from both the blood and the joint in the same patient. Morphologically and culturally the streptococci in each case have appeared to be identical. In a number of instances, however, the two strains isolated from different sources in the same patient have failed to cross-agglutinate. We believe that this apparent discrepancy can be explained by the marked tendency of these streptococci to undergo mutations. For example, it has been found that many typical strains isolated a year ago and preserved since then in blood broth at a low temperature have undergone certain cultural changes and are no longer agglutinated by either the serum from an arthritic patient or by immune rabbit serum. In other words, environmental differences may induce biologic variations in these streptococci not only *in vitro*, but also *in vivo*.

Experimental Arthritis. Several of the strains of streptococci which have been isolated from the blood and joints of patients with rheumatoid arthritis have been injected into various laboratory animals with the idea of determining their virulence and their capacity to produce an experimental arthritis. The typical strains differ somewhat in their virulence for mice, some killing a mouse in doses of 0.5 cc. of broth culture, while others have little or no effect. The typical strain is fairly virulent for rabbits; the sediment from 5 cc. of broth culture, when injected intravenously, usually kills the animal in forty-eight hours. On the other hand, doses as large as 10 cc. intravenously produce no symptoms in a ringtail or a rhesus monkey.

When rabbits are injected intravenously with sublethal doses of these streptococci a large proportion of them develop signs of arthritis in one or more joints. It is usually unnecessary to make more than one injection in order to produce joint symptoms. Usually, however, the rabbits tend to recover spontaneously after a few weeks. If a chronic progressive arthritis is desired it is often necessary to administer small intravenous injections of streptococcus culture from time to time. In rabbits with experimental arthritis the affected joints are swollen and when opened exude a slightly cloudy mucoid fluid. The periarticular tissues are thicker than

normal, and the synovial membrane is swollen and reddened. The condition of the cartilage depends on the duration and severity of the lesion. One of the most interesting observations made in connection with experimental arthritis is the high incidence of positive blood and joint cultures in the arthritic rabbits. In 6 arthritic rabbits subjected to blood cultures 5 yielded a streptococcus morphologically and culturally identical with the organism injected. In 5 rabbits with experimental arthritis fluid from one of the affected joints was cultured and a streptococcus identical with the organism originally injected was recovered in 4 of the 5 cases.

Microscopic sections through the affected joints of the rabbit presented a variable picture, depending on the duration of the arthritis. In cases of only a few weeks' duration the interarticular space contains mucus and broken-down cells and sometimes a considerable number of leukocytes. The synovial membrane is thickened and infiltrated with leukocytes and plasma cells, and there may be some superficial necrosis of the cartilage. Rabbits in which the arthritis has existed for several months show changes of a more chronic nature. There is less exudate in the joint cavity, and the synovial membrane takes on the appearance of chronic granulation tissue, the deeper part being composed of newly-formed connective tissue and the superficial part rich in cellular elements. The leukocytes are mostly lymphoid and plasma cells, together with a large number of macrophages.

When sections from one of the affected joints of a rabbit with experimental arthritis are compared with sections from a fusiform finger in man a striking similarity is seen in the two pictures. Indeed, without some method of identification, it would be impossible to tell which section came from the rabbit and which from the human lesions.

Fig. 1 shows the forepaws of a rabbit with experimental streptococcus arthritis of several weeks' duration. This rabbit received a single injection of 1 cc. of a "typical strain" intravenously. Many joints became affected. The photograph shows the wrists, which are swollen and deformed. The most interesting feature of the picture is the marked swelling of the metacarpal joints, which display a striking resemblance to the fusiform fingers of the human patient with rheumatoid arthritis. Radiographs of the forepaws of the rabbit (Fig. 2) show destruction of the cartilage, particularly in the right wrist, haziness of the metacarpal joint spaces and some deformity of the claws.

Summarizing, when a streptococcus of the type recovered so frequently from rheumatoid patients is injected intravenously into rabbits there results a subacute or chronic arthritis which simulates closely the same disease in man. And, furthermore, the same organism can frequently be recovered from the blood stream and from the affected joints of the arthritic rabbit.

If rheumatoid arthritis is a streptococcal infection, how do the

FIG. 1.—Front feet of a rabbit, two months after receiving an intravenous injection of 1 cc. of a twenty-four-hour broth culture of a "typical strain."

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FIG. 2.—Roentgen ray of same rabbit as in Fig. 1, two months after injection.

microörganisms gain access to the joints? Most students of this disease are prepared to admit today that some kind of focal infection is almost an essential prerequisite to the development of rheumatoid arthritis. It is true, of course, that focal infections are almost universal and that comparatively few people develop rheumatoid arthritis. It must be added, however, that in this climate nearly everyone at some time or other is a victim of some phase of rheumatic disease, be it arthritis, myositis, neuritis or what not. The occasional isolation of streptococci from the blood stream of non-arthritic patients with some focus of infection indicates that streptococci may sometimes be present in the circulating blood without exciting symptoms in the joints. In certain individuals, however, by reason of some constitutional tendency or as a result of sensitization to the streptococcus protein, the joints become infected and arthritis ensues. Gonococcal urethritis is an extremely common infection. Comparatively few patients develop gonococcal arthritis. This complication is probably dependent not so much on the occasional release of gonococci into the blood stream as it is upon the combination of gonococcus bacteriemia and susceptible joints. When rabbits are injected intravenously with even small doses of our typical strain of streptococcus a large proportion of them develop polyarthritis, but not for two or three weeks subsequent to the injection. These facts all point to the conclusion that to develop rheumatoid arthritis a patient must have: (1) A focus of infection; (2) a streptococcus bacteriemia; (3) a susceptibility to streptococcal infection of the joints. The exact nature of this susceptibility is not yet understood. Undoubtedly environmental factors, such as temperature and humidity play an important part in susceptibility to arthritis. Like rheumatic fever, the disease is rare in tropical countries. Nervous strain and physical and emotional exhaustion are important predisposing factors, and then, as in tuberculosis, heredity and a constitutional diathesis cannot be ignored.

Discussion. In this paper we have set forth the proposition that rheumatoid arthritis is a streptococcal infection, in which streptococci are discharged from some primary focus and, circulating from time to time in the blood stream, localize in certain joints and establish a secondary infection in them. In the investigations herein reported these streptococci have been actually demonstrated in the blood and joints of a high percentage of cases, and a disease almost identical with the human form has been produced in rabbits. If these results are corroborated by others there would seem to be little doubt left as to the streptococcal nature of this infection.

There has been much loose thinking and writing on the etiology of rheumatoid arthritis. Statements frequently seen in modern textbooks and articles to the effect that focal infection is the cause of *some* cases of chronic arthritis, that intestinal putrefaction is responsible for *other* cases, or that various infectious diseases,

derangements of the circulatory system or of carbohydrate metabolism are responsible for still other cases, produce an understandable state of confusion in the mind of the student. The pathologic and clinical features of rheumatoid arthritis make it almost certain that the disease is a chronic infection. We have presented strong evidence that it is a streptococcus infection, and that according to the agglutination reactions it is caused, in a great majority of instances, by a specific strain of streptococcus. The ubiquitous character of the streptococcus is the one thing that militates against its acceptance as the cause of this disease; but the Staphylococcus aureus and pneumococcus Type IV are also ubiquitous, yet no one questions their virulence. The pathogenic properties of streptococci in many conditions other than arthritis are well authenticated, and the fact that an experimental arthritis can be produced so readily in rabbits with this particular strain speaks strongly against its innocent rôle in the blood stream in arthritis.

The contamination theory is hardly valid, because:

1. Streptococci are rarely encountered as contaminants in bacteriologic work. In our own laboratory we have repeatedly exposed plates for several hours at a time, but have never recovered streptococci from them.

2. If these streptococci were contaminants one would expect to find just as high an incidence of positive cultures in the controls as in the arthritic series. Such, however, was not the case.

3. In almost 50 per cent of the positive cultures both blood culture flasks yielded streptococci, a finding entirely inconsistent with the contamination theory.

The observations reported tend strongly to confirm the theory that rheumatoid arthritis is an infectious disease, caused in a high percentage of cases by a specific type of streptococcus which, after localization in a primary focus, is discharged from time to time in the blood stream and establishes metastatic infections in the joints.

Conclusions. The evidence for the streptococcal origin of rheumatoid arthritis may be summarized as follows:

1. Almost constant presence of streptococci in foci of infection.

2. Streptococci recoverable from blood in 62.3 per cent of rheumatoid patients; 3.9 per cent in pathologic controls; none in healthy controls.

3. Streptococci recoverable from affected joints in 67.3 per cent of rheumatoid patients; from blood or joint in 77 per cent; none from nonrheumatoid joints.

4. High agglutination of "typical strains" of streptococci with serums of 94 per cent of patients with rheumatoid arthritis.

5. Disappearance of agglutinins with recovery from symptoms of arthritis.

6. Biologic identity of streptococci recovered from blood, joint and focus of infection in the same patient, though there have been a number of exceptions to this rule.

7. Reproduction of rheumatoid arthritis in rabbits with "typical strains" of streptococci.

8. Recovery of same streptococci from blood and joints of arthritic rabbits.

9. Striking similarity of histologic changes in rabbits' joints to those in human rheumatoid joints.

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THE EFFECT OF IRON ON BLOOD FORMATION AS INFLUENCED BY CHANGING THE ACIDITY OF THE GASTRODUODENAL CONTENTS IN CERTAIN CASES OF ANEMIA.*†

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The literature contains many conflicting statements concerning the value of iron in the treatment of anemia. One among the many reasons for this disagreement is that there has been seldom utilized

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a way of determining within a short space of time the effect of iron upon the anemic patient. In man, studies concerning the influence of this element on anemia have been measured usually by changes in the concentration of red blood cells and hemoglobin and rarely have other methods been employed. In certain sorts of anemia there occurs a prompt response of reticulocytes to suitable doses of iron. This reaction when properly evaluated can serve as an indicator of the effectiveness of iron and can be utilized as in pernicious anemia to determine the potency of effective substances. An illustrative example of the favorable influence of moderately large doses of iron on blood production and the lack of effect of liver and liver extract potent in pernicious anemia in a case of chronic "secondary" anemia is shown in Fig. 1. This female patient had been anemic for years. She had achlorhydria. The anemia was intensified by bloodloss from the pelvis about twelve weeks before coming under observation.

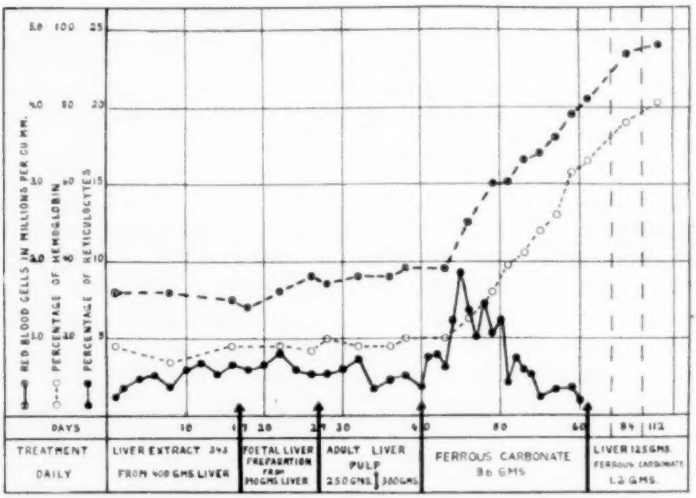
RED BLOOD CELLS IN MILLIONS PER CU MM.
PERCENTAGE OF HEMOGLOBIN
PERCENTAGE OF RETICULOCYTES
DAYS
TREATMENT DAILY
LIVER EXTRACT 3ss FROM 400 GMS LIVER
FOETAL LIVER PREPARATION 720 GMS LIVER
ADULT LIVER PULP 250 GMS. 300 GMS.
FERROUS CARBONATE 36 GMS
LIVER 125 GMS. FERROUS CARBONATE 1.2 GMS.

FIG. 1.—The ineffectiveness of liver preparations and the effectiveness of iron on a case of chronic "secondary" anemia.

The manner of absorption or utilization of iron from the gastrointestinal tract is a matter about which there is relatively little knowledge. It is probably largely absorbed in the duodenum and proximal jejunum. The excretion of iron is considered to take place chiefly in the cecum and Streicher's[1] recent observations lend support to this view. The factors concerned in regulating the intake, output and ultilization of iron, however, are unknown. A diminished iron absorption or utilization might be the result of many altered mechanisms.

It has been shown that the pH of the intestinal tract probably has an important influence on the absorption of calcium, phosphorus and possibly magnesium,[2, 3] and that these elements are absorbed more readily from an acid than an alkaline medium. Iron perhaps may behave similarly. Chronic chlorosis is a condition characterized by gastric achlorhydria in which iron deficiency seems evident since the anemia can be lessened dramatically with large, but not small, doses of iron. The lack of gastric acid may play a rôle in the production of this disease and certain other types of anemia because of failure of the gastric secretions to bring down the alkalinity of the contents of the upper intestine to a pH suitable for the best absorption of iron. With these facts and ideas in mind it was thought that perhaps if iron was fed in the presence of an alkaline or approximately neutral intestinal content, less response of the bone marrow would occur as measured by the course taken by the reticulocytes, than when an equal amount was fed in the presence of the most suitable acid reaction of the intestinal content.

Method of Study. In order to test out this theory the following procedures were carried out on 10 patients. The chemical reaction of the upper intestinal tract was maintained as nearly as possible at a constant pH when iron was fed. Ferric citrate, in doses varying according to circumstances, was dissolved in 50 cc. of hot water and added to 200 gm. of ground-up beefsteak, primarily prepared by digesting in *in vitro* for two hours at 37° C. with pepsin and hydrochloric acid at pH 3. Just before the addition of the iron this mixture was strained and used as such for an acid medium and for an alkaline or near-neutral medium when adjusted to between pH 7 and pH 8, with strong sodium hydroxid. This meal was administered through a tube passed into the patient's stomach. Observations have indicated[4] that such mixtures are suitable to maintain a given hydrogen-iron concentration of the duodenum for between one and a half and four hours, the longer periods occurring in patients with achlorhydria.

The experiment on each of the 10 cases was divided into four immediately successive periods. A preliminary control period was at once followed by a period during which the iron salt, in doses of from 0.5 to 2 gm., was fed daily with the alkaline or approximately neutral medium. The same daily dose of iron with the medium at the same pH was maintained in each given case for between nine and fifteen days, or until the reticulocytes had returned to a low level following a response. Then in the third period, which occupied from nine to sixteen days, the amount of the iron salt administered daily was the same, but was given in the meat mixture after adjustment to pH 3. With the exception of 1 case the meat mixture was not administered in the fourth period, but the dose of iron increased from small to large doses of from 4 to 6 gm. of either iron citrate or iron and ammonium citrate (these salts contain essentially the same

amount of iron) and fed in 3 daily doses with the "house diet." In 1 case during the fourth period the meat mixture was kept acid but the dose of iron increased four-fold.

Throughout the observations the reticulocytes were counted daily at the same hour. Usually 1000 red blood cells were counted in determining the percentage of reticulocytes. The counts were checked by 2 and sometimes 3 individuals. This procedure was employed particularly because relatively slight changes in percentage frequently were dealt with and it was recognized that slight changes were significant only if the counts were accurate and the course of the fluctuations was one of regularity. Every other day the hemoglobin concentration was determined by the Sahli method and the erythrocytes counted in the usual fashion.

The anemia of all of the 10 patients studied in the manner described above was distinctly chronic and of the so-called secondary type. Eight of the 10 patients were women and their anemia as well as the anemia of 1 male patient was associated with the partaking of a defective diet for a long period of time. There was a striking lack of meat and other animal protein foods in the diets and green vegetables and fruits were eaten sparingly if at all. The diets contained largely concentrated carbohydrate food. Several of the patients were great tea drinkers and stated that for days their appetite could be satisfied with frequent cups of this beverage and crackers or bread and butter throughout the day. In 3 of the 8 female patients chronic pelvic or rectal bloodloss combined with the rapid recurrence of pregnancy intensified the anemia. In 1 woman (Case 3) hypertension and chronic nephritis were pronounced and probably also played a rôle in the production of anemia. In 1 man (Case 9) hypertension and arteriosclerosis without definite nephritis existed. The anemia of the tenth patient, a male, was due to chronic bloodloss from hemorrhoids. He had not taken a defective diet. A hemorrhoidectomy was done one month before the observations began and no bloodloss had occurred during the month prior to therapy for the anemia.

Observations. In Figs. 2 and 3 are shown typical responses of the reticulocytes to small doses of iron when fed with beefsteak at an alkaline or nearly neutral pH and when subsequently fed with beefsteak at an acid pH. The figures also show a third response of the reticulocytes when the dose of iron was increased four- or twelve-fold. The data obtained on the cases not recorded in the figures were similar and are synopsized in Tables I and II.

Experience in pernicious anemia with the reticulocyte response to liver and other material effective in this condition[5, 6] has shown that the potency of a preparation can be estimated by the degree and character of this bone-marrow reaction. It is important to appreciate that in pernicious anemia the magnitude of the reticulocyte response is approximately inversely proportional to the red

blood-cell level if below 3,000,000 per c.mm. and often cannot be detected when the corpuscles are more numerous. The response

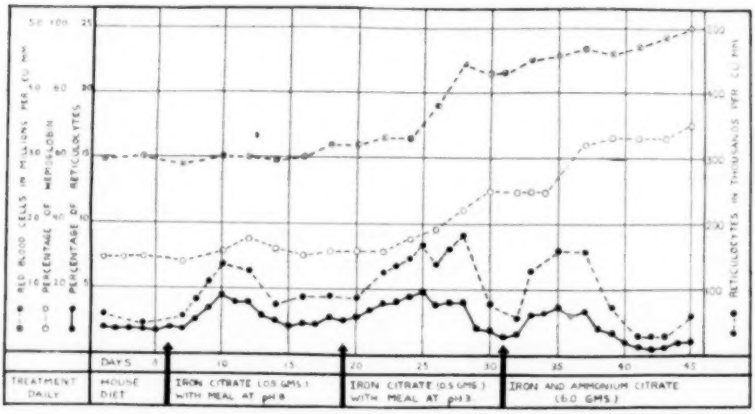
RED BLOOD CELLS IN MILLIONS PER CU MM
PERCENTAGE OF HEMOGLOBIN
PERCENTAGE OF RETICULOCYTES
RETICULOCYTES IN THOUSANDS PER CU MM
DAYS
TREATMENT DAILY
HOUSE DIET
IRON CITRATE (0.5 GMS.) WITH MEAL AT pH 8
IRON CITRATE (0.5 GMS.) WITH MEAL AT pH 3
IRON AND AMMONIUM CITRATE (6.0 GMS.)

FIG. 2.—The effect of administering iron with meat meal at pH 8, pH 3 and in greatly augmented amount to a case of anemia due to a prolonged defective diet and chronic bloodloss. (Case 2, Tables I and II.)

depends within certain limits upon the total amount of material given rather than the daily dose. Apparently a somewhat similar state of affairs holds true for responses of reticulocytes induced by

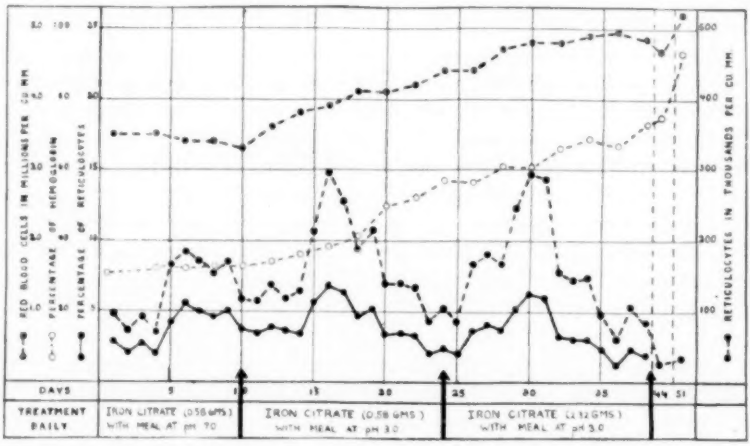
RED BLOOD CELLS IN MILLIONS PER CU MM
PERCENTAGE OF HEMOGLOBIN
PERCENTAGE OF RETICULOCYTES
RETICULOCYTES IN THOUSANDS PER CU MM
DAYS
TREATMENT DAILY
IRON CITRATE (0.56 GMS.) WITH MEAL AT pH 7.0
IRON CITRATE (0.56 GMS.) WITH MEAL AT pH 3.0
IRON CITRATE (1.12 GMS.) WITH MEAL AT pH 3.0

FIG. 3.—The effect of administering iron with meat meal at pH 7 and at pH 3 and in an augmented amount to a case of anemia due to prolonged defective diet and rapid recurrence of pregnancy. (Case 1, Tables I and II.)

iron in certain sorts of "secondary" anemia. If in pernicious anemia a sufficiently large daily amount of potent material is administered

no secondary rise of reticulocytes will follow even if the daily dose of potent substance is increased soon after the subsidence of the reticulocyte response. On the contrary, if submaximal amounts are administered and directly following the reticulocyte response maximal amounts are given a second rise of these cells will occur. Furthermore, the second response will be of a greater magnitude than the first if the amount of potent substance originally given was small, while if it was nearly maximal the second rise of the reticulocytes will be slight. Furthermore, if a greater amount of material is administered daily soon after a response induced by a smaller and submaximal amount of effective substance, usually a smaller reticulocyte response will occur than from that same amount of material given daily to an untreated case. It is believed that responses of reticulocytes to daily doses of iron may be interpreted in a similar manner to those induced in pernicious anemia. For this reason small doses of iron were used during the first periods of observation so that a comparative analysis could be made, since large doses of iron fed with an alkaline meal could cause a maximum reticulocyte reaction and if that were the case no second response could be demonstrated.

Definite responses of the bone marrow indicated by the course of the reticulocytes were obtained promptly following the ingestion of small doses of iron with meat at an alkaline or near-neutral pH. The particularly interesting result of the observations is the fact that subsequent reticulocyte responses, usually of a somewhat greater magnitude, occurred promptly when meat at a low pH (acid) was fed with the same dose of iron that had induced a few days before a response when fed with meat at a relatively high pH (alkaline or near-neutral). The third response of the reticulocytes that developed soon after the dose of iron was increased either in the presence or absence of the meat mixture at an acid pH shows that the reticulocyte responses were due to the iron and not to the meat just as liver preparations did not affect these cells in the case for which Fig. 1 gives data. By analogy with pernicious anemia the development of the second response is interpreted to indicate the greater potency of iron when fed with meat at an acid than at an alkaline or nearly neutral reaction.

The third reticulocyte responses give some indication of the relative inadequacy of small doses of iron and the value of optimal quantities, a subject of great practical importance that is not for discussion here. Although in some cases the change in the number of reticulocytes were of relatively small magnitude the data for each case, with the exception of Cases 9 and 10 and for the second response in Case 4, show that there occurred a distinct progressive rise and fall in these young corpuscles as is illustrated for Cases 1 and 2 in Figs. 2 and 3. The reticulocytes did not take a sporadic irregular course in any case. The lack of characteristic responses in Cases 9 and 10 may be associated with the relatively high level of the red

blood cells, the relatively low color index and the precise state of the bone marrow, although Case 8, with a similar degree of anemia, did show typical responses. The relatively pronounced responses in Case 1 are perhaps to be related to the fact that this patient's bone marrow was delivering more reticulocytes into the circulation when treatment was started than any of the other cases. It was expected that Case 6 with the most severe anemia would have the greatest reticulocyte responses but such was not the case, although data at hand do indicate that usually in the absence of infection or complications the more severe the anemia the greater the reticulocyte response to iron. Case 7 (Table I), treated daily with 2 gm. of iron citrate administrated with meat at pH 8, serves to illustrate by comparison with the cases given from 0.5 to 1 gm. how, even in the presence of an alkaline meal, larger doses of iron can cause greater reticulocyte responses than smaller doses. The dose, however, was not maximal because a second relatively small response took place soon after the acid meal was substituted for the alkaline one.

The time of onset and peak of the reticulocyte responses showed some variation. The responses to small doses of iron fed with meat at a high pH began between the fourth and seventh day and reached a peak between the fifth and ninth day, except in Case 3, where the height of the rise did not occur until the eleventh day. After feeding the same dose of iron with beefsteak at an acid pH on the average, the responses occurred slightly more rapidly. After increasing four- to twelve-fold the amount of iron, the reaction began on the third or fourth day, and the peak of the reticulocyte rise occurred between the fourth and sixth day. The shorter period may have occurred because the body already contained some of the iron that had been fed, and the bone marrow which had recently responded was thus in a state to react again more easily than when no iron at all had been given. On the other hand, the faster responses can be related directly to the effect of a more potent dose of iron entering the body.

The duration as well as the onset of the reticulocyte responses varied so that each patient was not fed iron with meat at a high or low pH for the same period of time. It took between nine and sixteen days from the commencement of the administration of iron with the meat mixture, adjusted to either a high or low pH, before the reticulocyte response had subsided sufficiently to permit a change in the type of therapy, so that conclusions could be drawn as to its effect on the reticulocytes.

It might have been expected that the patients with no free hydrochloric acid in their gastric contents after the injection of histamin would have shown a weaker response to iron in the presence of an alkaline meal than patients with a normal gastric analysis. However, the presence or absence of gastric hydrochloric acid did not appear to influence the results, as shown in Table I.

TABLE I.—RESPONSES OF RETICULOCYTES TO IRON FED WITH ALKALINE AND ACID MEALS AND TO DIFFERENT DOSES OF IRON.

Case	Sex.	Age.	Nature of case.	Gastric HCl.	Iron citrate in grams with meat meal daily.	Reticulocytes in per cent, upper figure; in thousands per c.mm., lower figure.				Augmented iron therapy, iron salt daily in grams.§	Reticulocytes in per cent, upper figure; in thousands per c.mm., lower figure.	
						Control period.*	At peak with alkaline meal.	Level before acid meal.†	At peak with acid meal.		Level before augmented iron therapy.†	At peak after augmented dose of iron.
1	F	36	Deficient diet 18 years; 4 pregnancies in 4 years; "anemic" 14 years	Free HCl only after histamin	0.58	2.3 80	5.5 195	3.5 115	6.7 295	2.32	2.0 90	6.2 290
2	F	40	Diet chiefly carbohydrate for years; chronic bloodloss from hemorrhoids	No HCl after histamin	0.5	1.6 45	4.5 135	2.5 85	4.6 180	6.0	1.5 35	3.6 158
3	F	50	Deficient diet for 3 years; chronic nephritis and hypertension	Normal	0.5	1.5 50	4.4 150	2.0 63	5.6 200	6.0	1.0 45	3.0 120
4	F	36	Defective diet; rapid recurrence of pregnancy	No HCl after histamin	1.0	1.0 33	5.4 200	2.0 90	3.0 126	6.0	1.8 75	3.8 185
5	F	..	Defective diet for 15 years	Normal	1.0	0.8 24	4.4 140	2.0 65	3.8 155	6.0	1.0 50	3.0 144
6	F	45	Defective diet for 8 years; slight chronic bloodloss from hemorrhoids	No HCl after histamin	1.0	1.3 20	6.0 105	1.3 22	6.1 134	6.0	2.5 77	5.0 155
7	M	34	Chronic bloodloss from hemorrhoids for 10 years; stopped a month before observations	Normal	2.0	1.0 28	13.0 350	2.2 83	4.6 188	‡		
8	F	36	Defective diet; "anemic since 17 years of age"	Free HCl only after histamin	1.0	0.6 25	2.8 126	1.8 73	4.4 180	6.0	1.4‡ 55	
9	M	65	Defective diet; hypertension; arteriosclerosis	Normal	0.5	0.8 36	1.2 54	1.0 46	2.4 95	4.0	1.0 47	2.6 120
10	F	41	Malnutrition for years; markedly underweight	Normal	0.5	0.6 23	1.2 45	1.0 38	2.4 100	6.0	1.2 50	2.0 90

* Figure given indicates level maintained during control periods of 5 days. Cells seldom varied as much as 1 per cent.

† Period of reticulocyte subsidence following previous iron meat meal. The number of days the alkaline or acid meal was fed varied from 9 to 16. This variation was necessary to permit proper observations as a second preparation could not be given wisely until at least a relative subsidence of the reticulocyte response.

‡ Discharged from hospital.

§ Iron and ammonium citrate was used in all cases except Case 1, where iron citrate was fed. These two salts contain essentially the same amount of iron.

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TABLE II.—RESPONSES OF RED BLOOD CELLS AND HEMOGLOBIN TO IRON FED FIRST WITH ALKALINE THEN WITH ACID MEALS AND LATER TO AUGMENTED DOSES OF IRON.

Case*	R.B.C. count, upper figure; hgb. per cent, lower figure; before treatment.†	Days after feeding iron with alkaline meal daily.‡||	R.B.C. count, upper figure; hgb. per cent, lower figure; at time indicated in previous column.	Days after feeding iron with acid meal daily.‡||	R.B.C. count, upper figure; hgb. per cent, lower figure; at time indicated in previous column.	After 10 days of augmented dose iron.||
1	3.5 35	10	3.3 38	13	4.3 57	4.8 64
2	3.0 28	13	3.2 31	12	4.1 48	4.7 65
3	3.0 40	15	3.2 45	10	3.6 58	4.3§ 70
4	3.3 36	14	4.1 50	11	4.2 57	4.8 75
5	3.0 40	12	3.4 47	14	4.7 65	5.0 80
6	1.5 12	12	1.7 17	16	3.0 36	3.8 47
7	2.3 38	15	3.8 70	16	5.0 90	
8	4.3 57	9	4.3 62	12	4.8 70	5.1 85
9	4.6 55	9	4.6 55	12	4.8 65	4.8 71
10	3.8 50	9	4.0 55	9	4.2 64	4.5 73

* Case numbers correspond to those in Table I.
† Figure given indicates level maintained during control period of 5 days.
‡ Time varies according to subsidence of reticulocyte response for reasons stated in footnote † in Table I.
§ Seven days instead of 10 days as in other cases.
|| Dose of iron given in Table I.

The strikingly beneficial effect of iron for the 10 patients, all of whom had been anemic for many months and often years, is reflected by the rapid increase of their red blood cells and hemoglobin (Table II). If optimal doses of iron had been given from the start the rate of increase would have been faster. Table II gives data for the concentration of hemoglobin and red blood cells ten days after the dose of iron was increased, but in all the cases the hemoglobin rapidly rose to over 85 per cent and the red blood cells to over 4,900,000 per c.mm. The increases of reticulocytes, total red blood cells and hemoglobin in Case 3 with hypertension and chronic nephritis were slower than in any other case, presumably due to the retarding influence of the damaged kidney on blood formation. The increase of blood in Case 7, where the anemia was due only to bloodloss, was faster than in any other case. This is probably attributable partly to the relatively large dose of iron and partly to the patient's good nutritional state. Unlike the other patients he had not taken an undesirable or defective diet for years.

The data suggest that the rate of blood formation was faster while the patients received meat at an acid pH than while they were given meat at a high pH with the same amount of iron, and that it was often still more rapid when the dose of iron was increased. In making such interpretations the facts noted below must be borne in mind. There must be at least five and often eight days of treatment before an effect on the total red blood cells or hemoglobin definitely can be detected. If the progressive manufacture of red blood cells and hemoglobin is already being induced by iron when a more potent form or greater amount of iron is given, then a comparison of the amount of blood manufactured in a given period of time under the latter conditions is not entirely comparable with the quantities produced in a similar amount of time from the beginning of iron therapy. Furthermore, in making comparisons of rates of blood formation it must be recalled, that, as a general rule, the higher the red blood cells and hemoglobin the slower is their rate of increase. The rate becomes slower, especially as the cells rise above 3,500,000 per c.mm. and the hemoglobin above 60 per cent. Thus, for example, if the corpuscles increase from 3,000,000 to 4,000,000 per c.mm. in response to a stimulus at the same rate as they did from 1,500,000 to 3,000,000 per c.mm. in response to a submaximal stimulus, then it may be taken as evidence that the second stimulus was greater than the first one.

The studies appear to indicate that soluble iron compounds are absorbed from the gastrointestinal tract or utilized more readily for blood formation when administered with acid than with alkaline meals. This conception is supported by an observation of Mitchell and Miller.[7] They found that the iron salts of spinach when rendered soluble by the addition of hydrochloric acid are

more effective in the treatment of nutritional anemia of animals than the insoluble salts.

Our observations are perhaps of physiologic interest and suggest that anemia can result from failure over a prolonged period of time in the adjustment of the contents of the upper intestinal tract to a most suitable pH for iron utilization, which could result among other ways from achylia gastrica. Under such circumstances a diet taken for a long time which contained suboptimal amounts of iron or was defective in other ways that hindered the utilization of iron could enhance the development of anemia.

The observations recorded also indicate the wisdom of prescribing optimal doses of iron for patients who can be benefited by this element. They do not imply that the drug must be given in an acid medium, for apparently if a sufficient dose is given in an alkaline medium suitable responses of the bone marrow will ensue. Probably in order to obtain an optimal effect a larger amount of iron salt must be given when the duodenal contents are alkaline than when they are acid.

Summary. Data are presented on 10 cases of "secondary" anemia especially associated with a prolonged defective diet or chronic bloodloss which responded rapidly and excellently to iron therapy.

The response of the bone marrow to iron administered daily first in small doses with an alkaline and then with an acid beefsteak meal and followed by a four- to twelve-fold increased dose of iron was studied by observing the course taken by the reticulocytes. Responses of reticulocytes occurred following each of the three procedures. The meat was used only as a medium to maintain the upper gastrointestinal contents at an approximately constant pH, and had no demonstrable effect on blood formation.

The responses to iron fed with beefsteak at a high pH were usually slightly less than those that followed a few days later from the administration of the same dose of iron with meat at a low pH. Thus it is concluded, particularly because the same dose of iron fed with beefsteak at an acid pH caused a prompt second response of reticulocytes, that iron is more potent for blood formation when absorbed from an acid than an alkaline medium within the intestinal tract.

The third responses induced by increased doses of iron indicate that the small doses were not optimal and serve to emphasize the importance of optimal doses of iron for patients with anemia that can be benefited by this element.

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THE EFFECT OF EPINEPHRIN IN ANGINA PECTORIS: WITH REPORT OF A CASE.*

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Recently Levine, Ernstene and Jacobson[1] have suggested that the effect of subcutaneously injected epinephrin may be used as a means of differentiating between true angina pectoris and other conditions attended by a pain similar to that of angina. They found that in a great majority of instances an injection of 1 cc. of 1 to 1000 epinephrin produces, in a patient who suffers from angina pectoris, a typical attack, accompanied by a sharper increase in systolic blood pressure, pulse pressure and pulse rate than is obtained in control subjects. Electrocardiographic changes observed by them consisted of a uniform increase in the amplitude of the *T* wave in Lead II in patients with angina, and the occurrence of ectopic beats of various types; one of their patients developed a transient ventricular tachycardia. In suggesting this procedure as a test, they say that it "would not be applicable when the diagnosis is certain, but rather in doubtful cases." They observed no serious consequences from the application of the procedure.

Our single experience with this test, we think, merits description.

Report of Case.—The patient, a Russian Jewess, aged forty-three years, was admitted to this hospital on February 13, 1930. Since July, 1929, she

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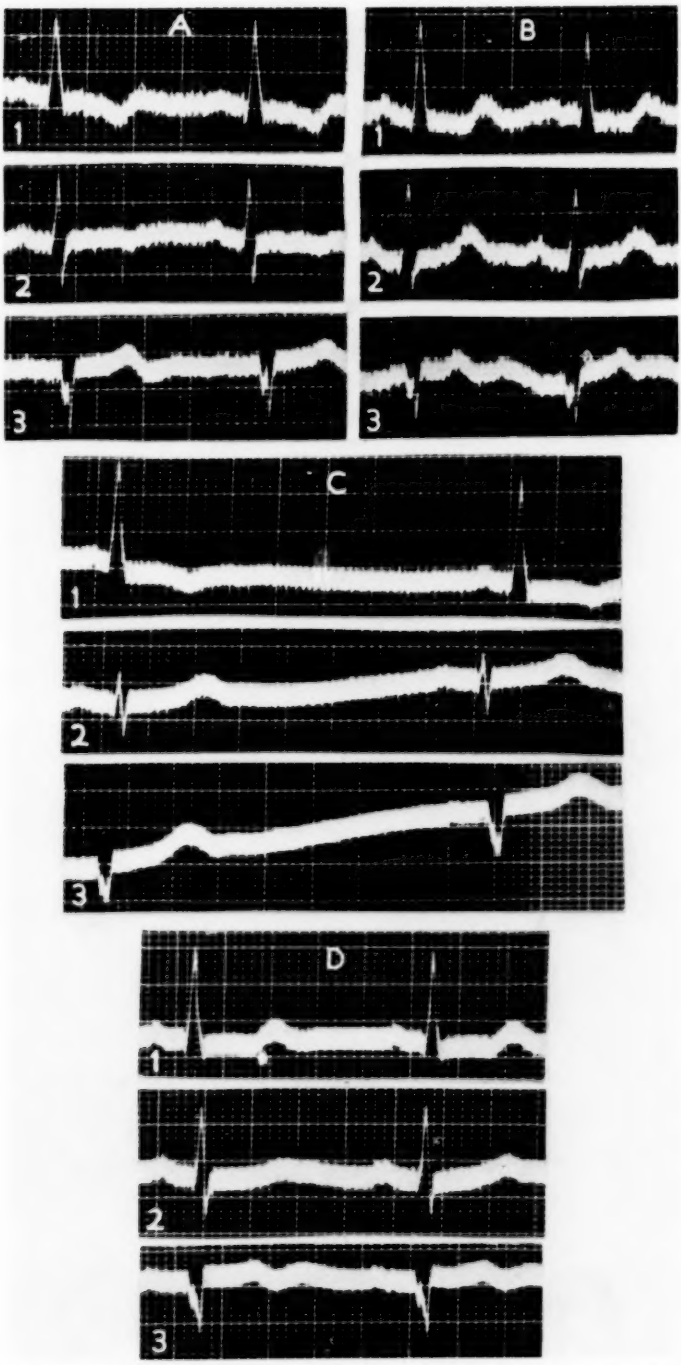

FIG. 1.—*A*, control tracing; *B*, during epinephrin action; *C*, during collapse; *D*, beginning recovery.

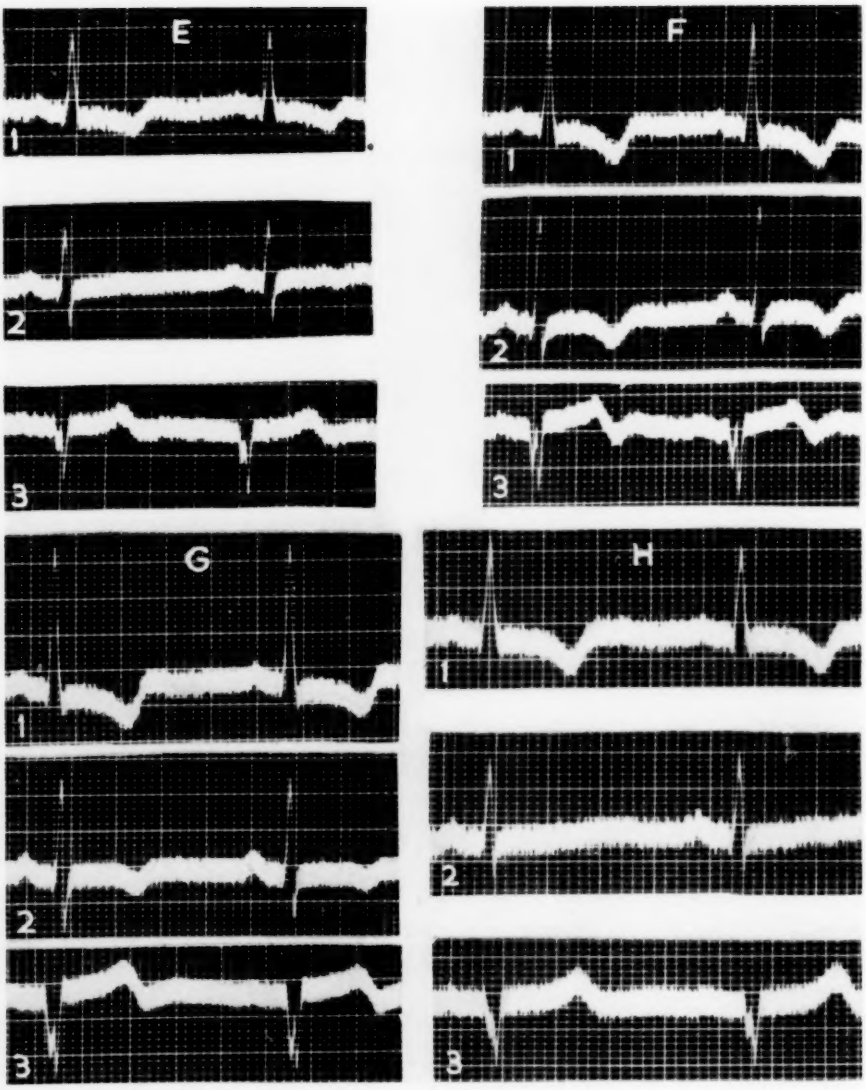

FIG. 2.—*E*, control, for comparison (same as Fig. 1-*A*); *F*, one day; *G*, three days; *H*, ten days, after test.

had experienced, at intervals of from a few days to four weeks, attacks of substernal pain which radiated down the left arm, over the left chest, and to the xiphoid process. The attacks were often, but not always, induced by exertion, and at times a good deal of activity was tolerated without pain. Nocturnal attacks occurred as well. After an attack, she sometimes noticed that the left hand was pale or bluish, swollen, and cold. There were no other symptoms of cardiac insufficiency. The bowels were constipated. She had lost 20 pounds in weight since the onset. She had undergone 9 laparotomies, beginning with an appendectomy in 1908; the others were for such conditions as intestinal obstruction, incarcerated incisional hernia, and adhesions. The menopause followed an operation in 1916.

The patient was 60½ inches tall and weighed 172 pounds. The blood pressure on admission was 210/110. The pulse rate was usually between 55 and 70 beats per minute, with frequent dropped beats. Orthodiagraphic measurements showed the heart and aorta to be of normal size (right base 3.8 cm., left base 8.8 cm.). The heart sounds were not remarkable except that the aortic second sound was accentuated. There was moderate retinal angiosclerosis; the peripheral arteries were not palpably thickened. There were no abnormal physical signs over the lungs, the liver was not palpable, the extremities were not edematous. The only additional positive findings were moderate dental caries, and numerous surgical scars on the abdomen.

The blood count was as follows: Hemoglobin, 87 per cent (Sahli); erythrocytes, 4,600,000; leukocytes, 5100; neutrophils, 64 per cent; lymphocytes, 31 per cent; monocytes, 3 per cent; eosinophils, 2 per cent. The blood urea nitrogen was 16 mg. per 100 cc. The blood Wassermann and Kahn tests were negative. The urine contained a faint trace of albumin and a few casts; the urinary specific gravity ranged as high as 1020. The phenolsulphonephthalein excretion after intramuscular injection of the dye was 45 per cent in two hours. By the van Slyke urea clearance test the renal function was 45 per cent of normal. Chest Roentgen ray showed a small circumscribed shadow in the middle of the right lung; its nature was uncertain, but the roentgenographic diagnosis was "probable benign tumor." The appearance was unchanged in successive examinations two months apart. In the electrocardiogram the ventricular rate was 67; there was sinoauricular block every 2 to 4 beats; the *Q–R–S* complexes were normal except for left axis deviation; the *T* waves were inverted in Lead I and flat in Lead II (Fig. 1–*A* shows the form of the complexes but not the arrhythmia.)

During her stay in the ward, the patient experienced several attacks of pain, usually without known exciting cause but on one occasion apparently induced by extraction of a tooth. The pain was virtually uninfluenced by amyl nitrite, and in at least one instance required morphin for relief. In the attack which followed the tooth-extraction, the blood pressure was 210/130, the pulse full and strong. She lay flat in bed, with one thin pillow. Her face was flushed, the features distorted; she gasped and moaned, rolled from side to side, beat her breast, clutched at her gown and at the bedclothes. The appearance was so different from the agonized immobility of classical Heberden's angina as to render us doubtful of the stenocardiac nature of the seizure.

The problem, then, was to distinguish between true angina pectoris and anginoid pain of neurotic origin. The lack of definite relation of attacks to exertion, to meals, or to mental stress, the behavior of the patients in the attack, and a general impression of a neurotic background all inclined us to suspect a functional basis. The epinephrin test suggested shortly before by Levine and his associates[1] naturally occurred to us. The indications which led us to apply the test were the prognostic importance of the differentiation and its influence upon treatment.

A condensed protocol of the test, performed on February 28, follows:

2.46 P.M. Radial pulse 75 per minute. Blood pressure 170/110. Control electrocardiogram (Fig. 1-*A*).

2.49 P.M. 1 cc. of 1 to 1000 epinephrin injected in left deltoid region. In the next ten minutes she remarked now and then that she felt as if she were going to have an attack. Then her premonitions began to subside, and it appeared that the test would prove negative. In order to avoid a false negative, at

3.08 P.M. the site of injection was vigorously massaged.

3.16 P.M. Severe pain in the xiphoid region, accompanied by the same behavior as previously observed in attacks. Radial pulse 86, regular. Blood pressure, 240/135. Electrocardiogram (Fig. 1-*B*).

3.22 P.M. Pain more severe. Inhalation of amyl nitrite, 1 pearl, in an attempt to terminate attack. No effect.

3.33 P.M. Morphin sulphate, $\frac{1}{4}$ gr. (H).

3.45 P.M. Pain slightly less, but still severe.

3.49 P.M. Inhalation of amyl nitrite.

4.16 P.M. Pain persists. Rate at apex 96. Blood pressure 168/115. Tablet of nitroglycerin, 1/100 gr., laid under tongue.

4.20 P.M. Patient vomited, collapsed, lost consciousness. Cyanotic. Respiration barely perceptible. Pulse imperceptible; sounds barely audible at apex, rate about 40. Blood pressure 80/60. Apparently moribund. Artificial respiration begun at once. Electrocardiogram (Fig. 1-*C*).

4.45 P.M. Began to recover consciousness and to answer questions. Pain recurred with return of consciousness.

5.10 P.M. Pain persists. Rate at apex 58, irregular. Blood pressure 120/60. Electrocardiogram (Fig. 1-*D*). Returned to ward.

12.00 Midnight.
Pain, hitherto present, had by this time practically disappeared. Radial pulse 64, irregular. Blood pressure 190/115.

The significant electrocardiographic tracings taken during the procedure have been grouped in Fig. 1;*A*, the control tracing has already been commented upon. Fig. 1-*B*, taken at the height of the epinephrin action, shows essentially the changes described by Levine and his associates, that is, the inverted T_1 became upright, and T_2 was markedly increased in height. In Fig. 1-*C*, taken during the collapse, there is a profound change in the ventricular complexes. Fig. 1-*D*, taken just after recovery of consciousness, is similar to the tracing taken at the height of epinephrin action.

The following day, the patient was rather weak and tired, but had no pain, and in general felt little or none the worse for her experience. An electrocardiogram (Fig. 2-*B*) showed *T* wave changes most marked in Lead II but present also in Leads I and III, which suggested myocardial infarction. There was no fever, leukocytosis, nor pericardial friction. Tracings taken three and ten days respectively after the test (Fig. 2, *G* and *H*) show a diminution of these new electrocardiographic features, but not quite complete return to the status of the control tracing. For about two weeks after the test the patient had no attacks; then they recurred, and at present, four and a half months later, her condition is about the same as when we first saw her.

Discussion. Since the originators of the test reported no such alarming occurrences, we reviewed the case to discover any differences in the patient or in the procedure which might have been

responsible for the severe reaction to epinephrin in the present instance. Three such possibilities present themselves:

1. The patient had sinoauricular block before the test.
2. She had marked hypertension, not present in any of the cases described by Levine and his associates.
3. The site of the injection was massaged—a variation from the prescribed technique.

Whether or not some or all of the factors may have operated to produce the terrific reaction, we cannot say.

Obviously, if epinephrin is capable of producing such an effect upon a patient with angina pectoris, much greater caution than we have been accustomed to observe is necessary in the general therapeutic use of the drug, when there is any suspicion that the patient also may have angina pectoris. In addition, we have been informed[2] of a case of bronchial asthma complicated by angina pectoris, in which the oral administration of ephedrin sulphate produced a severe, typical anginal attack on each of two occasions.

Summary. 1. In a single instance, subcutaneous injection of 1 cc. of 1 to 1000 epinephrin as a diagnostic test for angina pectoris resulted in a violent attack of substernal pain persisting for over eight hours; in collapse, unconsciousness, bradycardia, cessation of respiration, and a fall in blood pressure from 170/115 to 80/60; and in electrocardiographic changes suggesting added myocardial damage.

2. Therapeutic use of epinephrin in patients who may possibly have angina pectoris requires great care; this caution probably applies likewise to ephedrin.

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INSULIN SHOCK AND THE MYOCARDIUM.

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The sudden changes in the environment and the activity of the animal body exact marked fluctuations in metabolism and presuppose a readily available source of energy. Of the component principles of the diet, carbohydrates offer the most easily com-

bustible element. Accordingly, such foods constitute the primary source of energy which is expended in the main in muscular activity.

Among the muscles of the body none is so exacting in this relation as is the heart. The maintenance of its functional integrity is essential to life, and to this end the supply of available energy in the form of glucose must be continued without interruption. The actual needs of the myocardium for glucose have been variously estimated. Evans[1] calculated that the normal heart obtains one-third of its energy from the oxidation of carbohydrates. Hepburn and Latchford[2] quote figures for the consumption of glucose per gram of heart weight per hour as derived by various workers on rabbits ranging from zero to 7.1 mg. As evidence of the difficulties of the problem the following experience may be quoted. In 1912 Knowlton and Starling[3] reported the utilization of 4 mg. of glucose per gram of dog's heart per hour. A year later Patterson and Starling[4] refuted the earlier results and attributed the error to an unsuspected ability of the myocardium to store glycogen. The utilization of glucose by the heart varies with the experimental animal.[2,5] Cruickshank and Patterson[6] and others[5] developed the interesting circumstance of the heart's utilization of its contained glycogen before taking up the glucose of perfusate.

The utilization of sugar by the diabetic heart has been the subject of considerable study. Cruickshank and Patterson[6] concluded that the glycogen content of the myocardium was in inverse proportion to its utilization. There was no constancy to the failure of utilization in the diabetic heart in these studies. According to their figures, the normal heart utilizes 1.87 mg. per gram per hour, whereas the diabetic heart burns 0.9 mg. As early as 1912 Knowlton and Starling[3] proved that the addition of a pancreatic extract to the circulating fluid of a diabetic animal restored the power of utilization of sugar to the heart. MacLean and Smedley[7] confirmed this observation. With the advent of insulin Hepburn and Latchford[2] repeated this work and found the average consumption of glucose by the isolated perfused rabbit's heart to be 0.87 mg. per gram per hour. The addition of insulin increased this figure to 3.06 mg.

In clinical diabetes there is a notorious tendency to atherosclerosis. Indeed, recent studies[8] have indicated an increasing incidence of complications arising from this source. Insulin has clearly met the basic need in the control of carbohydrate metabolism. Yet the insidious factors leading to the sclerotic changes in the vascular bed definitely limit the conquest of the disease. There is no restriction to the distribution of this process, and importantly the coronary system partakes of the general changes. A vicious cycle is established in the myocardial nutrition. With increasing demands for effort come decreasing supplies of available energy in the form of combustible glucose.

With this circumstance in mind it has seemed logical to investigate the myocardium for evidence of adverse reactions to insulin, since this agent leads to such profound depression of the blood-sugar levels. Cannon and his associates[9,10] attempt a division of the manifestations of insulin shock under two causal heads, namely, hypoglycemia and sympathetic stimulation. They feel that the pallor, tachycardia, pupillary dilatation and profuse sweating of insulin shock may well result from sympathetic discharge. In this relation the failure of pulse rise on the administration of insulin after adrenalectomy is cited as proof of the absence of a direct action of insulin on the heart. With intact adrenals the fall of the blood sugar to between 0.1 and 0.07 per cent is attended by an increase in the pulse rate that is interpreted as a protective mechanism through which sugar may be mobilized by sympathetic activity from the liver. Inadequate hepatic reserve or too much insulin may lead to convulsions and coma, or even to death. From the present standpoint it should be noted that these observers remarked a rise of the pulse rate prior to any other manifestation of hypoglycemia and a subsidence of the same on the injection of glucose.

Tissue deprivation of glucose would, therefore, seem an early source of symptoms under insulin therapy, regardless of whether an adrenal or a sympathetic intermediary be admitted or not. Heténvi,[11] working with rabbits, determined low levels of the cardiac glucose of 63 and 76 mg. after twenty-four hours' starvation, when the blood-sugar readings were 103 and 118 mg. respectively. The lowest level of glucose in the heart after 20 units of insulin was 68 mg. and occurred one hundred and eighty-five minutes after the injection, at which time the blood sugar registered only 44 mg. Lower values for the blood sugar were obtained after convulsions from insulin, but the glucose of the heart was not proportionally decreased. With coma from insulin there appeared in two isolated experiments to be an appreciable recovery of both the blood and the heart sugar. The further details of this elaborate research are irrelevant to the present study except to note the inordinate depression of the skeletal muscle sugar under insulin as compared with the starvation figures. The hepatic content of sugar was more conspicuously affected in percentage fall, although the actual figures under the same conditions were by no means as low as those of the skeletal and the cardiac muscle.

If the matter of sugar deprivation or other factors influencing the circulation in insulin shock has any practical importance the literature of the past eight years should be replete with clinical experiences relating to its adverse circulatory effects. Such is not strictly the case, although sufficient clinical evidence may be adduced from these sources to warrant further attention to this serious question. As early as 1923 Gigon[12] reported the death of a diabetic patient, suffering from cardiac decompensation, after three doses of insulin.

This observer concludes, "Bei Patienten mit schweren Herzkrankheiten soll kein Insulin gegeben werden." Nicely and Edmondson[13] related in detail two clinical cases in which frank decompensation attended the administration of insulin. The recovery of both of these patients under the judicious use of orange juice plus smaller covering dosage of insulin and digitalis led to the hypothesis that the myocardial incompetency had, in part at least, resulted from an undernutrition of the heart muscle through depletion of the cardiac and bodily reserve of glycogen. Reinwein[14] further emphasized this matter by similar experiences on the exhibition of insulin to two diabetic patients in decompensation. The relief of both subjects on the withdrawal of insulin plus appropriate circulatory support impressed the necessity for caution in the use of insulin in such patients. Quite recently Turner[15] has recorded the occurrence of anginal attacks concurrent with and dependent upon insulin shock. The establishment of such a causal relation is entirely in agreement with the position of Budingen[16] and other continental workers.

In view of the early appearance of tachycardia in insulin reactions, as pointed out by Cannon and his associates,[9,10] it has been natural that particular attention should have been directed to a study of the pulse and blood pressure under these conditions. Indeed, so dramatically may the vasomotor system be affected that certain cases of hyperinsulinism as reported by John[17] may be mistaken for hyperthyroidism. The normal human being reacts to insulin by an increase in the pulse rate,[18,19,20] but there is no constancy to this reaction. Indeed, Kogan[21] established the reverse condition, that is, slowing of the heart, in frogs and rabbits. Weichmann and Koch[22] found an acceleration of the pulse rate in a majority of patients (8 of 13), but enough exceptions to render their judgment equivocal. Marked bradycardia has been recorded after the injection of insulin in isolated clinical instances by Fletcher and Campbell,[18] Kogan[21] and Gottstein and Bohe[23] among others.

Even less agreement as to the blood-pressure reaction to insulin is found in the literature. Sufficient observations upon man are available to render recourse to experimental evidence unnecessary. Fletcher and Campbell[18] remarked an occasional fall in the blood pressure on the administration of insulin. As a rule, their observations indicated that the blood pressure was sustained under insulin. Lyman, Nicholls and McCann[19] found a slight tendency for an elevation of the systolic pressure and a fall of the diastolic pressure. For example, one individual with initial readings of 100 systolic and 65 diastolic was given insulin (5 units), whereupon the blood pressure registered systolic 140 and diastolic 56. On the other hand, Weinberger and Hotzman[24] determined a downward trend of the blood pressure, not, however, paralleling the fall in the blood sugar. Kusnetzow[25] and others have postulated an antagonism between adrenalin and insulin in this relation. Weichmann and Koch[22] found a decrease in the systolic pressure in 18 of 22 observa-

tions and all showed a decrease in the diastolic pressure. These workers determined four instances of transitory aortic diastolic murmurs in individuals where the diastolic pressure was disproportionately depressed. Interestingly Klemperer and Strisower[26] made a clinical study of the effect of insulin on the blood pressure in a series of individuals grouped as follows: (*a*) Diabetes mellitus with high blood pressure; (*b*) pure hypertension without renal symptoms; (*c*) diabetes mellitus without elevated blood pressure; (*d*) normal. The percentage decrease was greatest in the diabetics with hypertension and least in the normal individual.

Important as are these observations, from the fundamental nature of affairs, it has seemed that electrocardiography should furnish the most conclusive evidence of a possible insulin effect upon the heart. Very few references to this phase of the subject are to be found in the English or the American medical literature; but continental studies are legion and sufficiently in accord to carry conviction. On the frog's isolated heart Citron[27] noted that insulin added to the perfusate brought about a decrease in the normal negativity of the *T* wave, a lengthening of the *P–R* interval and a widened *Q–R–S* with a somewhat lower *R* wave. Atropin did not abolish these electrocardiographic changes in the frog's heart. Frey[28] remarked extrasystoles without compensatory pauses in the frog's heart under insulin; but, importantly, he added the development of a shortened refractory period on the use of insulin. On the other hand, Beskow[29] and Collazo and Händel[30] were unable to demonstrate any influence of insulin upon the frog's normal or isolated heart. With another experimental animal, the rabbit, Haynal[31] determined the inversion of the *T* wave after the injection of insulin. This change was a progressive one from the normal upright form to flatness in ten minutes and to negativity in twenty-nine minutes after insulin. In addition to the characteristic *T* wave change in the rabbit's electrocardiogram under insulin, Haynal remarked a diminution of the *R* wave in many instances, but rarely was the *P* wave affected. Extrasystoles also appear in the rabbit's heart under the influence of insulin. Studies[32,33,34,35] upon the dog concur in these details; furthermore, Okashima and Ohkuni[36] indicate that the existence of a direct parallelism between the degree of the blood-sugar fall and the change in the *T* wave. Certainly in two of their plotted curves such a relationship would seem to exist; too, the suggested antagonism between insulin and adrenalin is borne out by coincident rises in the blood sugar and the *T* wave from their depressed levels of the insulin effect after the injection of adrenalin. These data are rather scanty; while suggestive, it is not felt that they can in any sense displace the contradictory evidence of Haynal and others.

The first electrocardiographic studies of the insulin reaction in man were those of Wittgenstein and Mendel[33] in 1924. These workers noted the same tendency of the *T* wave toward negativity which they had remarked in the dog. In one of their cases these

changes were induced in one subject by 100 units, after 45 units had failed to induce a deviation of the *T* wave. The most comprehensive studies upon this phase of the subject to date have been those of Haynal,[31,34,37] who with his associates has placed the question upon a sound clinical basis. In the first place, a lessening of the amplitude of the *R* waves was noted with the increased pulse rate of the insulin reaction. The *T* wave became lower and diphasic. At this point the injection of glucose intravenously slowed the cardiac rate without increasing the height of the *R* waves; but there was a delayed partial recovery of the normal form of the *T* wave. No direct parallelism between the blood-sugar level and the faults in conduction could be established by these workers.[37] Their final contribution and that of Schäffer, Bucka and Friedländer[38] entered more adequately into the profound conduction changes on the administration of insulin to patients with definite myocardial injury. Such serious faults of conduction, as extrasystoles, auricular fibrillation, dropped beats, bundle-branch block and alternans, were noted under these circumstances and constitute the strongest grounds for further study in this field.

Present Investigations. Accordingly the cardiovascular reactions of a group of diabetic patients to insulin shock have been investigated. Routine pulse, blood pressure and electrocardiographic studies have been made in 11 patients during the height of their clinical manifestations of insulin shock, at which time simultaneous venipuncture gave accurate information as to the glycemic state. As a control, similar observations were made in periods of complete freedom from symptoms, preferably at such times as the urine showed traces of sugar. All 11 patients of this group were diabetic, but 1 of them suffered from diabetes in association with acromegaly. The age range was from fifteen to sixty years, and there were 6 males and 5 females. In none of these individuals were there subjective or objective evidences of organic cardiac disease, although in several subjects varying degrees of sclerosis were demonstrable in the peripheral arteries.

Thirteen electrocardiograms were made on 11 patients during insulin shock. Twelve are available for analysis, but the thirteenth did not have a blood-sugar control. Hence it is excluded when a subdivision is made on the basis of the glycemic state. Of the remaining 12, 8 had a true hypoglycemia, or a reading of less than 70 mg. of glucose per 100 cc. of blood, at the time of the manifestations of insulin shock.

A comparison of the data obtained by studies during shock and in the control interval has been made under the following classification:

1. All patients showing clinical shock.
2. True hypoglycemic patients only.
3. Clinical insulin shock without hypoglycemia.

From the experience of earlier observers it was gathered that more appreciable changes might occur in the amplitude of the component waves of the electrocardiogram than in any other detail of these curves. Accordingly a standard method of measuring the curves, with a direct comparison of the tracings of each case, is used. The measurements (to 0.1 mm.) are then compared, and recorded as being reduced during shock, the same, or increased over the normal.

Unfortunately the data obtained from the blood-pressure observations at the time of shock and during a control period are not considered comparable, due to the inability of the same person to make all of the readings and the fact that the control blood pressures were not routinely taken at the time of the "normal" electrocardiogram. From the figures obtained, however, comparisons are made of the systolic blood pressure, the diastolic blood pressure and the pulse pressure at the contrasting periods, but for clarity they have been omitted from the charts.

The figures in Chart I are those obtained from a comparison of the measurements of all of the electrocardiograms taken during insulin shock with those of the normal period.

CHART I.—INSULIN SHOCK. (13 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				P wave.			*R* wave.			*T* wave.		
				Leads.			Leads.			Leads.		
		A–V cond.	*I–V* cond.	I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	6 46%	4	10 77%	7 54%	5 38%	5 38%	4	4	4	1	3	3
Decreased in shock	4	3	3	5 38%	5 38%	7 54%	3	6 46%	5	10 77%	9 69%	8 62%
Increased in shock	3	6 46%	..	1	3	1	6 46%	3	4	2	1	2

NOTE.—Percentage figures (of the totals) will be found in these charts only where deemed significant.

The most notable circumstance is the regularity of a decrease in the height of the *T* wave in all three leads. Seventy-seven per cent, 69 per cent and 62 per cent of the cases show, in Leads I, II and III respectively, a decreased amplitude of this wave. The greatest decreases were 2, 3 and 2 mm. for Leads I, II and III respectively. There is a tendency also for the *P* waves to be decreased in height, but this is less marked. In fact in Lead I, 54 per cent of the subjects show an absence of any change in this factor. The greatest decreases

were 0.5, 0.5 and 3.2 mm. for Leads I, II and III respectively. P_3 became diphasic in four tracings and inverted in two.

In 46 per cent of the tracings there is an increase in the auriculoventricular conduction time (greatest increase, 0.06 second), or twice as many cases as showed a decrease (greatest decrease, 0.04 second), whereas 77 per cent show no change in the intraventricular conduction time. The height of the *R* wave is increased most frequently (46 per cent) in Lead I and decreased most frequently in Lead II (46 per cent). The greatest increases in Leads I, II and III were 2.5, 2 and 3 mm. respectively, and the greatest decreases were 2.5, 5 and 3.5 mm. for the same leads.

The blood-pressure changes in insulin shock for the entire group show a tendency for the systolic (60 per cent of cases) as well as the diastolic (70 per cent) readings to be decreased, with no consistent change in the pulse pressure. A larger group (46 per cent) show a failure of alteration in the pulse rate in insulin shock than either increase or decrease in the rate.

In Chart II the eight tracings accompanied by true hypoglycemia are compared with the normal on the same patient.

CHART II.—INSULIN SHOCK WITH TRUE HYPOGLYCEMIA. (8 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				P wave.			*R* wave.			*T* wave.		
				Leads.			Leads.			Leads.		
		A-V cond.	*I-V* cond.	I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	4 50%	2	6 75%	4 50%	4 50%	3	2	2	2	..	2	1
Decreased in shock	2	2	2	3	3	5 62%	2	4 50%	4 50%	8 100%	6 75%	5 62%
Increased in shock	2	4 50%	..	1	1	..	4 50%	2	2	..	..	2

When the clinical picture of insulin shock is attended by hypoglycemia the electrocardiographic changes would appear more decisive. The *T* waves are depressed in 100 per cent of all tracings in Lead I and in 75 per cent and 62 per cent of Leads II and III respectively. The maximum decreases in Leads I, II and III were 2, 3 and 1.7 mm. respectively. One of the *T* waves in Lead I and two in Lead II became diphasic, and yet another in Lead III became inverted. The same relative tendency to depression of the *P* wave pertains as in the larger series. The pulse response and the conduction changes are likewise comparable. It was remarked that the

greatest changes in amplitude of the component waves and in the conduction time were to be found almost invariably in the true hypoglycemic series.

The patients who had clinical evidence of insulin shock, but whose blood-sugar readings were above 70 mg. per 100 cc. are 4 in number and 3 of these are in the age group of over forty years. The fourth patient is seventeen years of age and his blood sugar was 88 mg. at the time of his manifestations of insulin shock. This figure is from 100 to 150 mg. below his usual level, and he is apparently very sensitive to blood-sugar changes.

The electrocardiographic data for this series of patients with insulin shock but without hypoglycemia are given in Chart III.

CHART III.—INSULIN SHOCK WITHOUT HYPOGLYCEMIA. (4 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				P wave.			*R* wave.			*T* wave.		
				Leads.			Leads.			Leads.		
		A–V cond.	*I–V* cond.	I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	2	2	3 75%	2	1	1	2	1	2	1	1	1
Decreased in shock	2	1	1	2	2	2	1	2	1	2	3 75%	3 75%
Increased in shock	..	1	..	..	1	1	1	1	1	1		

In this group the height of the *P* waves tends to be decreased, but the most marked constant change is again noted in the reduction of the amplitude of the *T* waves. The maximum reductions in Leads I, II and III were 1, 0.5 and 2 mm. respectively. One *T* wave became diphasic, one inverted, but another became less inverted. Conduction-time changes are not notable. The changes of the patient, aged seventeen years, are the most consistently comparable to those of the hypoglycemic series. However, the numbers herein considered are too small to admit of generalization.

The possible influence of atherosclerosis upon the noted electrocardiographic changes led to a further subdivision of the group into those under (6 cases) and those above forty years of age (7 cases). These data are grouped in Charts IV and V.

An analysis shows a definitely increased tendency in the cases below forty years to have a delayed *A–V* conduction time. The effect of insulin shock upon the *P* and *R* waves varies little in the two groups, except that P_1 and P_3 are decreased during insulin

shock more commonly in those cases over forty years of age. Much more definite decreases in the height of T waves are noted in the younger group in the Leads I and III, where 100 and 83 per cent of the cases show a diminution as compared with 57 and 43 per cent in the older group. The greatest decreases also occurred in in the former group, where the average decrease was 0.7 mm. in Lead I and 0.8 mm. in Lead III, as compared with 0.5 mm. (Lead I) and 0.2 mm. (Lead III) in the older group.

CHART IV.—LESS THAN FORTY YEARS OF AGE. (6 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				P wave.			*R* wave.			*T* wave.		
				Leads.			Leads.			Leads.		
		A–V cond.	*I–V* cond.	I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	2	..	3	3	4	2	2	2	1	..	2	
Decreased in shock	3	1	3	2	2 33%	3	2	3 50%	3	6 100%	4 66%	5 83%
Increased in shock	1	5 83%	..	1	..	1	2	1	2	..	..	1

CHART V.—MORE THAN FORTY YEARS OF AGE. (7 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				P wave.			*R* wave.			*T* wave.		
				Leads.			Leads.			Leads.		
		A–V cond.	*I–V* cond.	I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	4	4	7 100%	4	1	3	2	2	3	1	1	3
Decreased in shock	1	2	..	3 43%	3	4 57%	1	3	2	4 57%	5 71%	3 43%
Increased in shock	2	1	..	..	3	..	4 57%	2	2	2	1	1

The blood-pressure studies in these groups show a systolic decrease in 80 per cent of the older group, whereas the younger patients show no definite change. There are no significant differences in the diastolic and pulse-pressure readings of the two groups.

Slurring of the Q–R–S complexes in two or more leads, inversion of T_1 and T_2, low voltage, delayed conduction time and depressed

S–T segments are generally accepted electrocardiographic criteria of myocardial change. By these standards, the heart muscle of only one of this group can be adjudged normal, and interestingly this individual is the diabetic with acromegaly. Slurring of the *Q–R–S* complex in two or more leads was the most common abnormality encountered in this group of diabetics with supposedly normal heart muscle. More significance attaches to this circumstance when it is appreciated that two youths aged fifteen and seventeen years are included in the group under consideration.

From an analysis of the electrocardiographic responses to insulin shock, both in this study and in previous reports, the changes in the *T* wave obviously constitute the most constant finding. Other alterations occur, but they are neither constant nor common. In fact many of them would seem to depend upon the preëxistence of some serious myocardial lesions,[13,39] but flattening and inversion of the *T* wave occur commonly in the apparently normal heart as a response to insulin shock. Of the duration of these changes there is no exact information, but even the most serious alterations in conduction apparently are transient.

Every gradation of pathologic and prognostic significance has been given to inversion of the *T* wave of the electrocardiogram. The occurrence of this change in certain leads has been noted on the administration of quinidin, digitalis and epinephrin. Smith[39] determined negativity of the *T* wave on ligation of the left coronary artery in dogs, and Parkinson and Bedford[40] concluded from a comprehensive study of the electrocardiographic course of coronary thrombosis that the negative *T* wave even in Lead III may constitute the sole *residuum* of an earlier cardiac infarction. While heartily subscribing to this possibility, such a grave background for any appreciable proportion of the instances of inverted *T* waves would seem highly improbable. Katz,[41] in an exhaustive *critique* of the matter, decided that the "inverted *T* wave is not pathognomonic of any clinical entity, but is rather to be regarded as the result of a disturbance in the pathway of retreat, which simulates persistence of activity in the apical region of the left ventricle, unless its cause can be shown to be a shifted anatomical axis or a changed capacity of the skin."

In his earlier work Haynal[34] leaned toward a hypoglycemic explanation for the electrocardiographic changes noted under insulin, but the report of Haynal, Vidovszky and Györgi[37] strongly supported a direct action upon the myocardium. Particularly is this position defended by their clinical experience of a failure of intravenous glucose injections to relieve the electrocardiographic changes. Schäffer, Bucka and Friedländer[38] used the same evidence in favor of a direct action of insulin upon the myocardium. Indeed, prophylactic doses of glucose intravenously have in their hands failed to prevent the *T* wave changes. On the other hand, both of these

groups of workers strongly recommended the cautious exhibition of insulin with adequate glucose to prevent hypoglycemia in diabetic patients with myocardial degeneration. Lauter and Baumann[42] suggested that the earliest reaction to insulin in the form of an increased minute output of the heart is not shock in the ordinary sense but an expression of carbohydrate need. Whatever the ultimate explanation may be, there is a growing sentiment in favor of Budingen's[16] practice in the use of glucose in myocardial affections. In view of his reports and isolated clinical experiences in other hands, advantage may be expected from the rational exhibition of glucose not only in the anginal type of cardiac distress, but also in congestive heart failure. If further evidence on this point be necessary, the remarkable success of Smith and his co-workers[43] in the relief of congestive heart failure by means of a high carbohydrate diet may be quoted. Such results serve to emphasize the importance of an available source of energy to the heart, and, given a fundamental error in the metabolism of the most important of these sources, glucose, an added significance attaches to the study of the myocardium in diabetes mellitus.

Summary. 1. As in diabetes mellitus there exists an inability of the tissues to utilize glucose, a certain handicap falls upon all tissues, including the heart, in the limitation of a readily available source of energy. Coupled with this disturbance in metabolism is a definite tendency for the development of atherosclerosis in these individuals. A serious obstacle to proper function is thereby thrown on the myocardium through impaired coronary circulation.

2. In the face of such disadvantages insulin imposes a further theoretical chance of injury through the induction of hypoglycemia, to which may be added other adverse effects. Experimental and clinical evidence indicates that this hazard is real, as is confirmed by the present study of 11 patients during insulin shock.

3. Particular importance attaches to the establishment of common changes in certain of the component waves of the electrocardiogram and to less common but more serious errors in conduction during insulin shock.

4. Because of the gravity of the changes noted in the presence of myocardial lesions, particular caution is enjoined in the use of insulin in such patients. Where any question as to myocardial competency exists, the avoidance of hypoglycemia must be insured by an adequate coverage of insulin through concomitant intravenous glucose injections, even though there is no agreement as to the causal relationship of the depressed blood sugar.

5. The practice of inducing insulin shock for whatever purpose is unphysiologic, and in view of possible myocardial injury its occurrence cannot be condoned if avoidable.

NOTE.—The technical assistance of Mrs. William A. Werrell is gratefully acknowledged.

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DIABETES MELLITUS.

A Review of 1073 Cases, 1919–1929.

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The following study was made for the purpose of organizing this material into a form whereby it would be available for comparison with the statistics of other observers; and it is concerned with a series of 1073 cases of diabetes taken from the Grace Hospital records and the office histories, between the years 1919 and 1929.

Each history has been gone over individually, and an effort made to classify the cases into the groups most suitable. As in any large

series of cases, difficulties arise in classification. The aim has been to keep the groups as sharply demarcated and as definite as possible. Naturally, some cases fall into more than one group, especially when one is dealing with etiologic factors and with complications. There is another factor of error which should be mentioned: some of the earlier records from the hospital and the clinic were incomplete, as the patients usually were admitted in coma, and did not revive sufficiently to answer questions.

The clinic cases, when compared with those of the private patients, showed some marked differences, especially in regard to heredity; this factor occurring with almost double frequency in the patients of superior intelligence, due to the individual's greater knowledge of the pertinent facts of the family history. No separation has been made between the cases before insulin and after its use was begun; the group will be restudied from this standpoint at the end of the ten-year period, and then will be compared with this review.

Age and Sex. In the entire series of 1073 cases, there were 379 males, and 694 females, a percentage of 35.3 and 64.7 respectively. The Jewish race contributed 370 cases, 34.5 per cent of the total. As may be seen from Table I, there was an almost equal incidence of males and females in the first three decades, after which the male incidence remains at about the same level from the age of thirty to sixty years, while there is a remarkable rise in the female incidence from the fourth to seventh decades. Thus, the greatest number of cases occurred in females between the ages of forty and sixty years, when there were only 148 males, against 388 females. It is interesting that below the age of thirty years, the males predominated by 69 to 66.

TABLE I.

Age group.	Males.	Females.	Total.	Per cent.
1	12	3	15	1.4
2	25	26	51	4.7
3	32	37	69	5.5
4	70	94	164	15.2
5	75	172	247	23.7
6	73	216	289	26.9
7	77	127	204	19.0
8	14	19	33	3.0
9	1	...	1	0.01
Total	379	694	1073	99.4

The highest incidence of the disease was found to be at the age of obesity, as has been stated by all observers, particularly Joslin,[1] and the almost double occurrence in the female past middle life would seem to point to some etiologic factor present at this time, and attributable, directly or indirectly, to sex. By far the greatest number of cases was in the obese female fifty to sixty years of age, when there were almost three times as many cases as were seen in any other period group. John,[2] in two series of 1000 cases each,

found an almost equal incidence in males and females in the first group (January, 1927); and a female preponderance of 36.9 per cent in the second 1000 cases (August, 1928). He was unable to explain this variation.

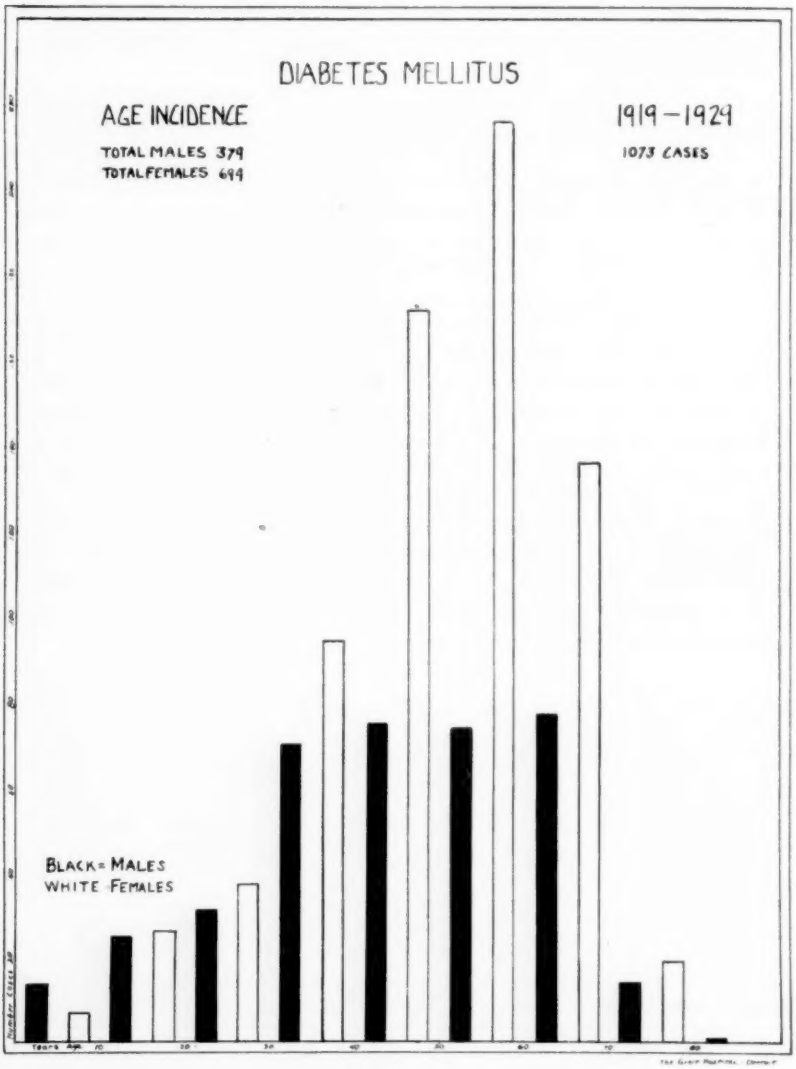

CHART I.

Onset Factors. The histories were gone over in detail to find what symptoms were present at onset, and as nearly as possible

to determine the etiologic factor. At times it was impossible to make any decision as to the latter, and in such instances these precipitating factors, although not necessarily etiologic in the production of the disease, were grouped as being of causal importance. They were coincidental at least, possibly predisposing causes. The result of this grouping is shown below:

TABLE II.

Onset factor.	Cases.	Per cent.
Obesity	619	57.8
Acute infection	228	21.2
Heredity	159	14.8
Physical or mental strain	127	11.8
Goiter	96	8.9
Furuncle	61	5.7
Tonsillitis	39	3.6
Syphilis	35	3.0
Carbuncle	25	2.3

We wish to call especial attention to the fact that 3.9 per cent of these patients suffered from an attack of tonsillitis some time near the onset of their symptoms; also the physical and mental-strain group. Whether or not there is such a group at all is a debatable question. Joslin, in a personal interview, stated that he had seen no case of diabetes arising from mental strain. We feel that there is such a group, and have endeavored to put into it all such cases which might be so classified, that we might see how large this group would be. The result was rather startling, as there were 127 such cases. It is well known that glycosuria does occur in periods of mental stress in apparently normal individuals. During the recent stock-market flurry we received 3 cases of glycosuria of this type in one week. One of these proved to be a transient glycosuria, with a normal glucose-tolerance curve; the second was a renal glycosuric; while the third, Case 902, was not unusual. This man's symptoms, intense thirst and polyuria, began with great intensity immediately following reverses on the stock market. His blood sugar the following day was 400 mg., and the urine was loaded with sugar, acetone, and diacetic acid. His carbohydrate tolerance at the beginning of treatment was only 50 gm. daily, but two months later he had increased this amount to 400 gm. It is quite probable that he was a potential diabetic before this occurrence, but he had had many urinary examinations previously, and had never shown any sugar. The point we wish to make is that the anxiety and mental strain were sufficient to tip over his carbohydrate metabolism to such an extent that he developed typical diabetic symptoms and laboratory findings. He was in a moderately severe acidosis when first seen, and might easily have gone into coma. We believe that this nervous factor is not regarded as being of sufficient importance, and wish to call attention to it. The stress of multiple operations is likewise of some importance, and we have thrown these cases into this same group.

Goiter also shows a rather high incidence in this series. Again, it is impossible to state that it is causative. We have had several severe cases of diabetes, with coincident goiter, which have been markedly improved by thyroidectomy. Any series in this locality would show a high goiter incidence, due to the endemic character of this disease. Our experience has been that the diabetes associated usually is benefited by goiter management, although we would hesitate to say the diabetes is primarily caused by the hyperthyroidism. It should be considered as a predisposing cause.

Heredity and familial factors were found to be present in 159 cases, or 14.8 per cent of the total. Joslin[3] gives 21 per cent; John[2] found 9.7 per cent, and 10 per cent in his two series. Von Noorden, in 1917 (cited by Joslin), gave the occurrence of this factor as 25.4 per cent. There is considerable variation in the reports from various clinics, a difference caused mainly by the different types of patient treated. We found a great difference in this regard between the patients treated at the clinic and those seen in the office. The average charity patient whom we see often does not know from what his parents died, and but extremely few have any idea about affairs of the remoteness of grandparents. It is interesting to note that last October, when Dr. Joslin visited our clinic at the Grace Hospital, out of 14 diabetic children in the gathering, 8 had diabetic relatives. All authors have remarked about the familial occurrence of this disease, and it is probable that could we obtain complete family records, we would be startled at the result. Our office patients had a familial history in 65 per cent of cases; the clinic patients show only 33 per cent.

Acute infections have been variously attributed to be a cause of diabetes. We found 228 patients, or 21.2 per cent who had a history of having had some acute infection at or reasonably close to the date of onset of their diabetes. It is remarkable that in childhood, when the acute infections are at their height, diabetes is comparatively rare. It occurs chiefly in the era of degenerative diseases. In no instance have we been able to determine that the diabetes was directly due to an infection. Some children developed symptoms following the occurrence of several of the childhood diseases in rapid succession. Dr. F. A. Weiser has a case in an adult in which symptoms began with abdominal cramps, fever and vomiting.

The most marked onset factor in this series, as in all others, is the occurrence of obesity, 57.8 per cent of all our cases. By obesity we mean at least 20 per cent overweight for height. Joslin found 77 per cent who were overweight at onset.[5] He states that overheight in children is as important as overweight in the adult; we have found this principle to be true in our private patients, but were unable to obtain complete records in all the hospital cases.

"Syphilis is a rarity in a diabetic clinic," states Joslin (p. 173). Rosenbloom,[7] found 11.5 per cent among a series of 139 cases. Dr.

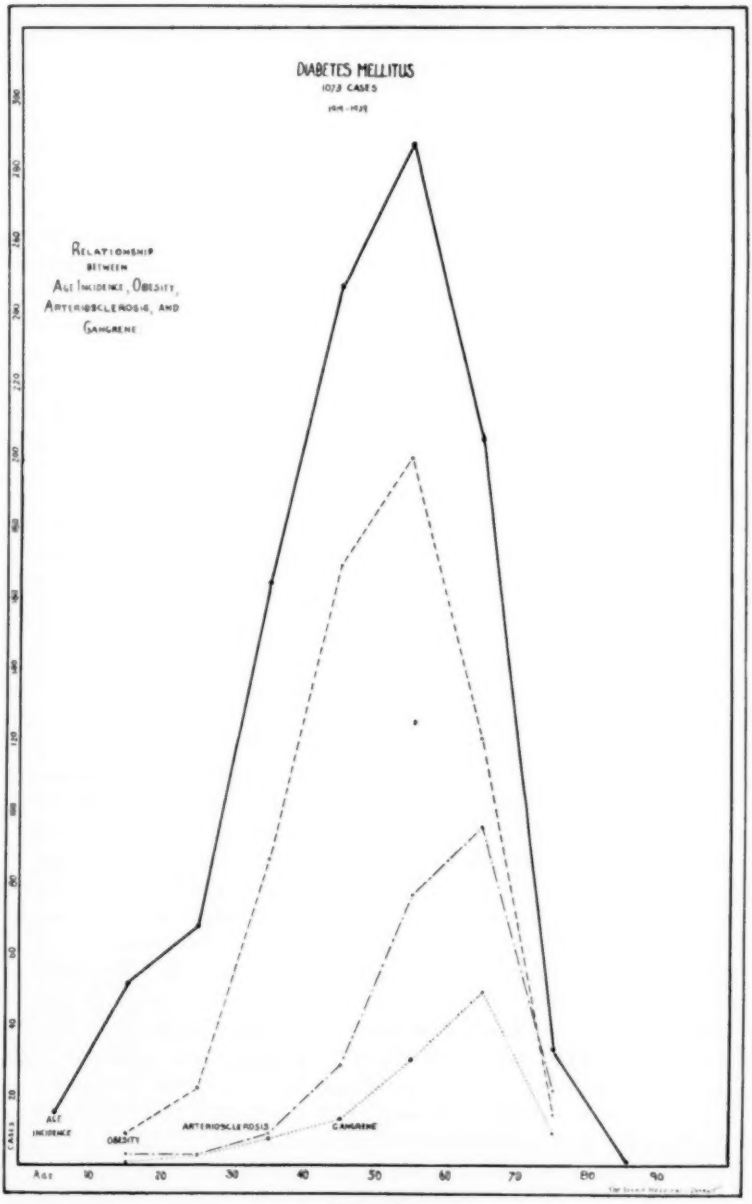
DIABETES MELLITUS
1073 CASES
RELATIONSHIP
BETWEEN
AGE INCIDENCE, OBESITY,
ARTERIOSCLEROSIS, AND
GANGRENE
AGE
INCIDENCE
OBESITY
ARTERIOSCLEROSIS
GANGRENE
CASES
AGE
10
20
30
40
50
60
70
80
90

CHART II.

F. S. Perkin recently stated that the incidence of lues among the diabetics at the Receiving Hospital is very close to the figure. Our own series contains 35 cases, or 3 per cent, having a positive (4+) Wassermann. A differentiation must be made between two groups of glycosurics with lues; namely, the syphilitic who develops diabetes, and the diabetic who develops syphilis. Those syphilitics who develop diabetes will do well on antiluetic treatment, and their diabetes will usually be benefited by such treatment. The diabetic who contracts lues, will do very badly on antiluetic treatment. This lack of differentiation is probably the reason some men have stated that diabetes contraindicates the use of arsphenamin. We have had no difficulty in this regard except with the diabetic who contracts syphilis, and this occurrence is fortunately rare. One case (No. 853) deserves especial mention. This patient died in coma which followed severe convulsions, seemingly brought on originally by hypoglycemia, but not relieved by glucose. The blood sugar shortly before death was 350 mg., and the urine contained sugar, but no acid bodies. Autopsy disclosed generalized cerebral and vascular syphilis. It is stated in the literature (Joslin[8]) that diabetes inhibits the development of tertiary and neural manifestations of syphilis, and it is possible that in this case good diabetic management flared up the latent process, resulting in convulsions, and ultimately death. Such cases should be watched for, and reported in the future. Warthin[9] reported 6 cases of latent syphilis in 1916 which were associated with diabetes.

Relationship Between Obesity, Age-incidence, Arteriosclerosis and Gangrene. An interesting parallelism is shown in Chart II between age-incidence, obesity, arteriosclerosis, and gangrene. The curve for age incidence and obesity is of almost identical shape, with the peak of the curve falling in the forty to sixty-year age group. The height for arteriosclerosis is reached at fifty-five to sixty-five years of age; while gangrene, as would be expected, was highest at sixty-five years. It should be noted that the younger age groups were not free from arteriosclerosis which occurred as early as the second decade. This quartet, obesity, diabetes, arteriosclerosis, and gangrene follow each other so closely that they all seem to be dependent upon similar factors.

Complications. Diabetes has been well called a disease of complications. An idea of the frequency of occurrence of these may be gained by perusing the table on page 59.

As with most groups, it seems that the greatest difficulty was with the arteriosclerosis cases. It was likewise the highest percentage complication which we had, namely 21.5 per cent. It begins early, and rises to almost the same peak as the occurrence of diabetes. One would expect to find more cases in the later age groups, but the duration of the diabetes seems to be an important factor. Almost half of the arteriosclerotic cases developed gan-

grene eventually. Only 13.2 per cent showed hypertension with their arteriosclerosis; some cases having the greatest involvement, had normal or subnormal blood pressures. About one-fourth of the cases of gangrene came eventually to amputation. Two patients have had both legs amputated at the thigh. Another has lost both legs and one arm. These patients are usually not very severe diabetics, and as a rule do well after the source of their infection has been removed. We feel very acutely the need of an effectual method of preventing gangrene in these patients. We have had them develop gangrene of an extremity while under good hospital control, a very distressing accident.

TABLE III.

Complications.	1 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80 to 89.	Total.	Per cent.
Acute infections	8	16	16	30	59	59	34	6	0	127	11.8
Abscess	0	7	6	8	13	14	11	2	0	61	5.7
Carbuncle	0	1	4	5	6	4	4	1	0	25	2.3
Acromegaly	0	0	0	1	2	0	0	0	0	3	0.28
Goiter	0	5	13	17	21	26	12	2	0	96	8.9
Arteriosclerosis	0	3	3	9	28	76	95	21	0	233	21.5
Gangrene	0	3	3	8	13	30	49	9	0	113	10.7
Coma	6	29	22	15	19	19	15	2	0	127	11.8
Lues	0	0	2	6	8	13	4	0	0	33	3.0
Tuberculosis	1	3	4	8	7	9	10	0	0	42	4.0
Uremia	0	1	0	1	6	5	2	0	0	15	1.4
Nephritis	0	1	1	2	6	7	2	0	0	19	1.7
Retinitis	0	0	3	7	10	16	9	2	0	47	4.3
Cataract	0	0	1	1	2	22	13	2	0	41	3.8
Otitis media	0	2	0	6	5	11	6	1	0	31	2.8
Hypertension	0	1	2	9	24	53	45	8	0	142	13.2
Tonsillitis	1	7	3	9	10	5	3	1	0	39	3.6
Neuritis	0	0	2	3	8	22	16	2	0	53	5.0
Amputation	0	1	1	2	4	16	19	5	0	48	4.4
Death	3	10	11	8	20	31	31	11	0	125	11.5
										1073	100.0

Coma occurred 127 times in 11.8 per cent of the cases. It is especially troublesome among the younger age groups, possibly because they are the more severe diabetics and more apt to be indiscreet in diet. Coma reached its highest incidence during the second decade, arteriosclerosis in the sixth.

From thirty years of age onward coma maintains an almost constant level in this series. There have been fewer cases in the past year. Even the less intelligent patients in the clinic are apparently learning about the pitfalls to be avoided. They now come in in acidosis; and they know that they have diacetic acid in the urine; they are aware of its significance, and want something done about it. This is a very gratifying change, and we feel that it is due to the

constant repetition of the teaching in the clinic. They are taught the diacetic acid test as well as Benedict's sugar test.

It is not necessary to use glucose in the treatment of the average case of coma or acidosis. The patient usually has enough excess of sugar, and if sufficient insulin is given, he can overcome his acidosis without added sugar. Occasionally we use it when the patient becomes sugar-free and still has acid bodies present; but then we give food instead of glucose. Large doses of insulin are likewise

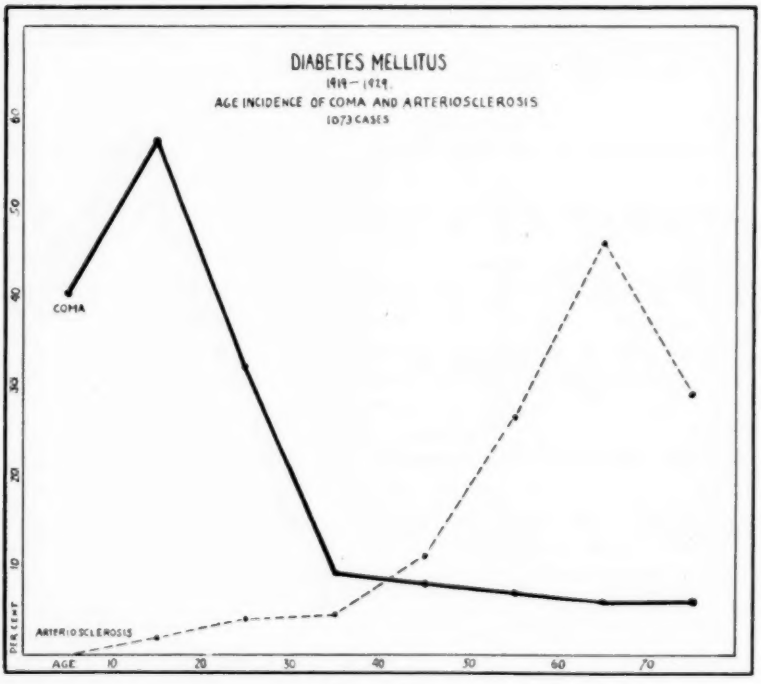

CHART III.

usually unnecessary. The patient should be put to bed, kept warm, given fluid, insulin and caffein. We rarely use doses of insulin to exceed 20 units, but give it often, depending upon the glycosuria as a guide. Too much insulin may cause anuria.

The acute infections, tonsillitis, abscesses and furuncles usually have responded to treatment with no particular difficulty since the advent of insulin. In making this study, it was noted that the cases before the insulin era almost without exception died; most of the hospital admissions at that time were for gangrene or coma. This state of affairs has changed remarkably since 1923, and we are interested in making this study again after ten years of insulin.

There will unquestionably be quite a difference in the mortality rate by eliminating those cases before 1923.

"Neuritis," using the term in a rather vague way, has been productive of a great amount of difficulty in treatment. By this term, we here mean that group of cases who complain incessantly and continually about pains in various regions, especially the lower extremities. Some of these people actually have severe pain, and are difficult to manage, but show few signs. It is a symptom not confined to the older age groups. Fifty-three patients, 5 per cent of the group, have had this symptom. It is probably not a true neuritis, in most cases. The pain is not stationary, but as a rule first one place and then another, and there are no physical findings of note. One patient (No. 717), an arteriosclerotic seventy years of age, had such severe pains in the legs that she eventually came to amputation before relief could be obtained. Another (No. 353), a female aged fifty years, a mild diabetic, was completely relieved by an epidural injection made by Dr. Bunten. She recently died after a three days' illness with Ludwig's angina, but was sugar-free during her last illness. It is noteworthy that these patients complain of more pain when they have high blood sugars and an uncontrolled diabetes. They should be warned however, that the pain is apt to persist after normal blood sugar levels are obtained, perhaps for several months after, but as a rule they do get better. Another woman (No. 840) had severe pain in the legs for six months after ideal control with normal blood sugars and a sugar-free urine. No other treatment was administered; she was persistent with her diabetes management, and eventually became free from pain. It is necessary to keep these patients sugar-free and under good control for long periods, and we feel that occasional lapses of treatment with glycosuria cause return of pain. Woltman and Wilder[10] recently reported a series of cases in which a definite neuritis with necrosis of the nerve was found at autopsy. It is likely that some of these cases in which pain persists would fall into that group.

Tuberculosis occurred in 42 cases, 4 per cent of the total. These patients do very well as soon as the diabetes is controlled, and an adequate diet, with rest, is provided. As in the presence of any type of infection, they will require more insulin. We have never seen the insulin do any harm, and are feeding them very high diets, with enough insulin to keep them sugar-free. Any diabetic who is not doing well should have his chest examined by Roentgen ray, if no other explanation can be found for poor progress. We have discovered several unsuspected cases by this procedure. One patient (No. 462) was found with a generalized tuberculosis of the lungs and with multiple tuberculous ulcers of the bowel and was still up and working. He also had a positive Wassermann and some spinal cord symptoms. His mother is diabetic.

Insulin. There were 315 insulin cases, 29.4 per cent of the series. The percentage would be higher if we excluded the cases treated before 1923. At present about one-third of all our patients are taking insulin, another third take it irregularly for emergency use, as during infections, and a final third have been able to do without it entirely. We have had no so-called insulin refractory cases. There have been 2 deaths from the improper use of insulin. In 1 case a patient was given 90 units by his physician, and died on admission to the hospital. The other case became rapidly sugar-free following the drainage of a large abscess, went into insulin coma with previously excreted sugar in the bladder urine, and was given more insulin when this bladder specimen was examined and sugar found. These unfortunate accidents impress one with the care necessary in teaching patients, nurses and even physicians. One must be sure that the bladder is empty before being certain of glycosuria, as the urine then being excreted may be sugar free, but on mixing with previously excreted urine in the bladder, may give a false positive reaction.

We seldom find it necessary to use large doses of insulin, and consider it safer to use the smaller doses, repeated at more frequent intervals as found necessary. Most of our patients take but 2 doses daily, and rarely over 20 units at a dose. Reactions have been considerably more frequent in the past year and a half due to the reduction in the amount of fat in the diets. This fat seems to have a buffering effect on the insulin, and to some extent gives it a slower action. After taking this factor into consideration, the difficulty was obviated, and we find that we are now using less insulin on these patients.

Cholesterol. For the past year we have made more and more use of this valuable estimation. It seems to be a fair measure of the success of the diabetes management. The highest reading in this group was 722 mg. per 100 cc. Those patients doing well have normal cholesterol figures. Our technician, Miss Edna Olsen, has been doing cholesterol estimations along with the glucose-tolerance tests, and finds an interesting rise in the cholesterol with the blood sugar rise, and she is reporting this more completely. We believe the cholesterol determination is valuable in detecting the occasional patient who starves for a day before coming to the clinic, in order to give a good blood sugar report, and, with Helen Hunt,[11] that it is of even more value than the blood sugar in determining control of diabetes.

Blood Sugar. The highest blood sugar in this series was 725 mg. The lowest was 30 mg. (No. 732), the latter with no symptoms of hypoglycemia. John, in 1927,[12] reported hypoglycemic reactions with high blood sugars; and this condition has occurred in several patients of this series. One case was especially interesting. Case No. 671, a deaf mute, was admitted because of the difficulty

met with in keeping her between hypoglycemic coma and acidosis, following a pleurisy with effusion a few months previously. Her blood sugar was taken at intervals of two hours, and found to fluctuate between 500 before breakfast, and 40 in midafternoon, when

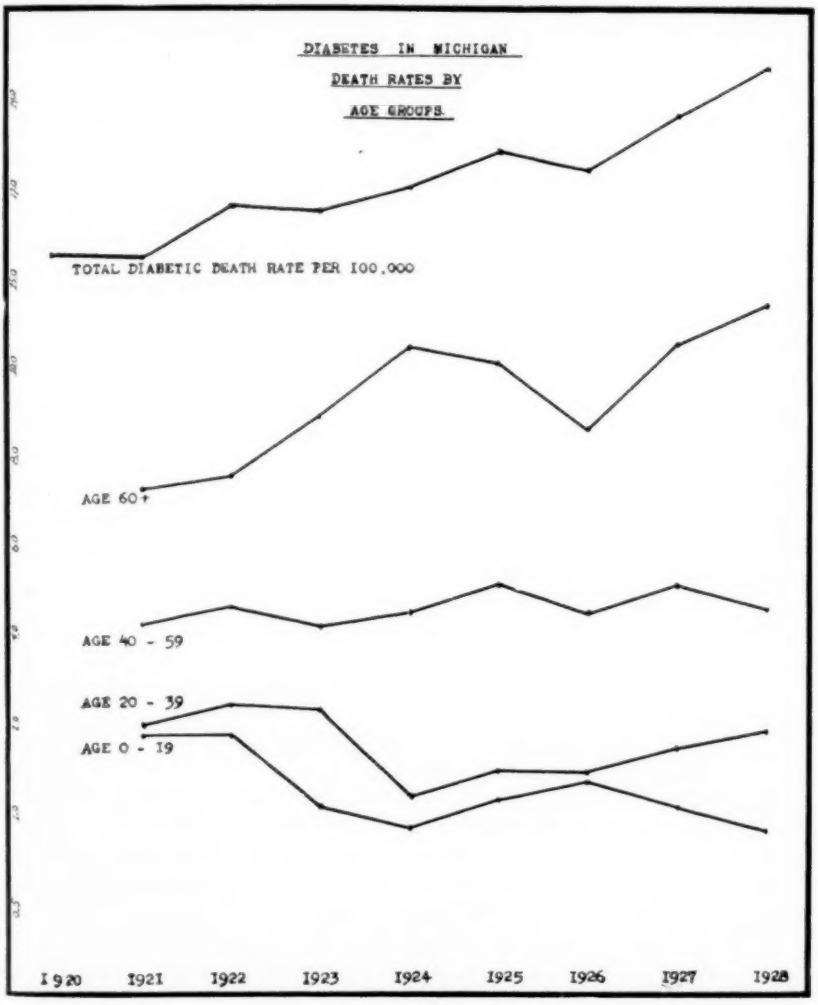

CHART IV.

she would have a severe insulin reaction. The insulin dosage was adjusted many times, but without overcoming the difficulty. Finally she was fed an equal meal every eight hours, and blood-sugar estimations continued each two hours as before, with the

result that the curve quickly smoothed out, and we were able to maintain her comfortably with practically normal blood sugar readings throughout the twenty-four hours, and with only one-half the amount of insulin formerly used. She continued to keep her meals as far apart as possible after discharge, and has continued to do well. Since this time we have used this method in several other cases who were difficult to maintain sugar-free, and it has worked quite well, except for the inconvenience of the unusual hours of eating.

Mortality. Including the heavy toll for the three years before the advent of insulin, the mortality for this series was 11.5 per cent. It is considerably less at the present time, but still leaves much to be desired. We have less coma, but arteriosclerosis and gangrene go onward, and the hospital beds are filled with these unfortunates. The general death-rate still continues to rise in spite of insulin, as shown by the appended chart of diabetes in the State of Michigan. If this chart is analyzed into age groups, it is seen that below the age of nineteen years there has been a goodly decline in the death rate since insulin. The total number of deaths below forty years of age also shows a very slight decline. From the fourth decade onward, the rate is rising. At least we have apparently been doing something for the youngsters, as this drop must be due to the decrease in the coma deaths. But arteriosclerosis and gangrene remain, and we are now carrying on the children long enough to develop these changes, when formerly they died in coma. The general death rate will continue to rise as long as we have no solution for the problem of arteriosclerosis.

Summary. 1. A series of 1073 cases of diabetes is presented.

2. There were twice as many females as males.

3. The age of obesity was the age of diabetes, of arteriosclerosis and of gangrene.

4. Diabetes may develop following excessive nervous and mental strain, and this type is usually mild.

5. Familial factors were found in 14.8 per cent, and there is a much higher incidence among the more intelligent classes.

6. Syphilis is probably not as uncommon among diabetics as has been supposed. A case of latent syphilis might possibly become activated under good diabetic management.

7. Coma and arteriosclerosis are the chief complications. The former may be eradicated by educational measures plus insulin. The latter remains as our toughest problem, and is the cause of the rising death rate from diabetes.

8. Insulin is necessary for about one-third of our diabetics, must be used temporarily for another third, while the remainder can get along without it. Large doses are usually not necessary. Glucose is not necessary in the treatment of most cases of coma.

9. The cholesterol determination has been of value in following the progress of cases.

10. A more nearly constant blood-sugar level may be obtained in some patients by feeding them every eight hours, and less insulin is used by so doing.

11. The mortality rate is still rising. Arteriosclerosis is now our greatest problem in diabetic management.

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HYPERTHYROIDISM AND ASSOCIATED PATHOLOGY.

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This article comprises a study of 12 necropsies on patients that suffered from hyperthyroidism. The series covers the period to 1930, from 1923, which year denoted the advent of iodin therapy.[1] It is therefore representative of what might be termed the iodin era of thyroid disease. Reports on the general pathology in hyperthyroidism antedate this period and consist mostly of those by Müller (1893),[2] Simmonds (1911),[3] Matti (1912),[4] Pettavel (1912),[5] Capelle and Bayer (1913),[6] Fahr (1916 and 1921),[7, 8] all of which are of value in affording an extensive summary and bibliography of the German literature, Blackford and Freligh (1916),[9] Goodpasture (1921),[10, 11] Wilson (1923),[12] and Holst (1923).[13] These reports also antedate the principal work on the association of the basal metabolic rate, and therefore lack one of the principal criteria for estimating the degree of thyroid overactivity.

The individual pathology of the thyroid gland was fully demonstrated by Marine.[14, 15, 16, 17] Marine pointed out that in dys-

thyroidism the essential physiologic disturbance is an insufficiency of iodin, that hyperplasia of the gland is compensatory, and that the degree of hyperplasia varies inversely with the iodin content. The so-called endemic goiter represents a persistent or recurring deficiency disease, a deficiency of iodin.

Clinical Data. Of the 12 cases, 3 died without operation. In Case 1, death occurred suddenly from auricular fibrillation and Cheyne-Stokes respiration, developing after a pre-operative subcutaneous injection of scopolamin and morphin. Case 2, with long-standing thyrotoxicosis and cardiac decompensation, was comatose on admission and died from auricular thromboses and multiple infarction. Case 7 died of subacute glomerular nephritis. None of the 3 showed thymicolymphatic hyperplasia. Of the 9 operative cases, 2 died clinically of postoperative storm and at autopsy showed thymicolymphatic hyperplasia, and 3 died with questionable postoperative storm but without thymicolymphatic hyperplasia at autopsy.

Sex and Age. Eleven were females, all married. The 1 male patient was 1 of the 2 cases dying of postoperative storm with thymicolymphatic hyperplasia. The most common age period at death was fifty to sixty, which decade includes 7 patients. One patient died at twenty-two years of age, 3 at forty to fifty years, and one at sixty-four years.

Duration. A striking feature in most instances is the long duration of goiter and symptoms. The longest history of goiter is thirty-five years; the shortest is three months. The longest duration of symptoms is sixteen years, questionably, but definitely eight years in the next; the shortest duration of symptoms is about two and a half months. Previous to the use of iodin, the group most liable to die in thyroid crisis or postoperative storm were those under thirty years of age, with fairly rapidly-developing disease, on an average of nine months' duration; Plummer showed that nine months was the duration period at which the greatest number of deaths occurred.[8]

Symptoms. Symptoms of thyroid overactivity were prominent in each case, and were accompanied by correspondingly high basal metabolic rates. The highest metabolic rate was +100, present in the youngest patient. Pre-operative iodin therapy brought a decreased rate in all cases.

Cardiac and Hypertensive State. Of the 12 cases, all had tachycardia, 7 had irregular rhythm listed as fibrillation, and 2 had marked irregularity and decompensation. Hypertension, with a blood pressure above 160, was present in 4 patients, aged, incidentally, forty-five to fifty-nine years; all 4 had thyrotoxicosis with fibrillation.

Pathologic Anatomy. *Thyroid.* The pathology of the thyroid glands in this series falls into two main groups. On the one hand are 7 cases, showing primary hyperplasia of the follicular epithelium.

Involution of the epithelium, which can occur spontaneously or after the administration of iodin, is considered present in an early stage when the epithelium is columnar and the colloid content of the follicles small, in a moderate stage when the epithelium is cuboidal and the colloid content moderate, and in a late stage when the epithelium is flat and the colloid content abundant. The remaining 5 cases, classified as endemic goiter, are characterized by irregular foci of hyperplasia and degenerative or involutional changes. Case 3 differs, however, by having multiple adenomatous foci, discretely encapsulated and undergoing secondary hyperplasia. The size of the gland was incomplete for most cases, lacking the single and combined weight of both operative and postmortem specimens. Furthermore the amount of thyroid tissue is by no means proportional to the severity of symptoms.

Heart. The largest heart weighs 510 gm., the second largest 500 gm., and each shows hypertrophy of the muscle fibers. In the first, aortic stenosis, and in the second, marked hypertension is probably the cause of the hypertrophy. The smallest heart weighs 230 gm. The average weight of the ten hearts, excluding the one affected by aortic stenosis and the one by hypertension, is 327 gm. The sizes of the hearts are roughly parallel to the duration of the disease by symptoms; but it should be noted that the higher blood pressures have a similar crude correspondence. With the exception of the scarred, stenosed aortic valve, suggestive of an old rheumatic endocarditis, in Case 9, valvular lesions were essentially absent.

Sclerotic changes in the coronary vessels are marked in 2 cases (1 and 3), each of whom was in the arteriosclerotic age, had hypertension and auricular fibrillation, and showed comparable sclerosis of the aorta and cardiac hypertrophy at autopsy.

Changes in the myocardium are of note in 3 cases. There is a small amount of sclerosis in Case 1, in addition to the marked hypertrophy, and also in Case 3. Case 2 had a moderate degree of sclerosis; each auricle, however, has a firm thrombus adherent to the appendage. Two cases (7 and 9), show myocardial changes that are apparently postrheumatic. Of the 2 patients dying with thymicolymphatic hyperplasia, in 1 (Case 5) interstitial edema and slight fraying and loss of striations suggest a slight toxic myocarditis; in the other (Case 12) the heart is essentially negative.

Aorta. Six of the 12 aortæ have some degree of arteriosclerosis; 6 are essentially normal. In 2 cases (1 and 3) fairly marked atheromatous changes, loss of elasticity, thickening of intima, and scattered calcified plaques are present. To some extent the cases with the more marked arteriosclerosis are those with the longest duration of thyroid disturbance; but it should be noted again that the higher blood pressures have a similar crude correspondence.

Kidneys. In only 2 cases are very marked renal changes present: several foci of infarction in Case 2 and subacute glomerular nephritis in Case 7. The older individuals have, in accordance with the age

and cardiovascular condition, a moderate degree of chronic vascular nephritis. The average weight of the kidneys is 139 gm.

Lungs. Changes occur mostly from postoperative complications or secondary to cardiac decompensation. Bronchopneumonia was a primary fatal factor in 4 instances, (Cases 4, 6, 10, 11) all postoperative deaths; Cases 10 and 11 had the inhalation type of bronchopneumonia with acute inflammatory reaction in bronchi and trachea. In 2 cases (3 and 7), bronchopneumonia was a contributing factor. In 3 cases chronic passive congestion is present, moderate in Case 1, which died suddenly on pre-operative preparation, fairly marked in Case 2, which had auricular thromboses and fibrillation, and very marked in Case 9, the only case to show numerous heart-failure cells. The 2 cases, dying in postoperative storm and showing thymicolymphatic hyperplasia, had injected, soggy lungs.

Liver. There are only minor pathologic changes. In one exception, Case 3, the liver is small, dense, weighs 960 gm., and has some cirrhosis suggesting a toxic or alcoholic basis.

Associated Endocrinopathy. Thymic hyperplasia is definitely present in 2 instances, both with primary hyperplasia of the thyroid.

In Case 12, the thymus weighs 40 gm., is wedge-shaped, measuring 10 cm. long, 4 cm. wide, 1 cm. thick, and in the body reached from above the sternoclavicular joint down to the third costal interspace. Microscopically, it has well-developed thymic tissue. There are generalized hyperplasia and congestion of the lymphatic system. But the spleen, pancreas, and adrenals are negative. In Case 5, moderate thymic hyperplasia is associated with mesenteric, intestinal, and splenic lymphoid hyperplasia; the pancreas and adrenals are negative. In the remaining cases, the thymus was not found at autopsy.

The spleens show various changes of chronic or recent congestion, in keeping with the cardiac state. The pancreases, adrenals, and ovaries are essentially normal.

Discussion and Literature. *Thyroid.* Of the two pathologic conditions of the thyroid comprising this series, the cases of primary hyperplasia have a history of goiter for three months to twelve years, or an average of four and two-third years, a history of symptoms for three months to three and a half years or an average of one and a half years. The cases of endemic goiter have a history of goiter for fifteen to thirty-five years, or an average of twenty-three years, a history of symptoms for nine months to sixteen years, or an average of five and a half years. In the first group the average duration from goiter to symptoms is three years, in the second or endemic goiters seventeen and a half years. It can be readily realized that a history of goiter of long duration, supplemented by a long period from goiter to onset of symptoms, is of definite clinical value in the differential diagnosis of these two types.

The severity of symptoms showed no definite differences in either group, and of the 8 cases with marked cardiac disturbance, 4 had

primary hyperplasia and 4 endemic goiters. The 2 cases dying in postoperative storm and showing thymicolymphatic hyperplasia had primary hyperplasia of the thyroid.

Cardiovascular System. In the estimation of the cardiovascular pathology, there should be no failure to make proper allowance for lesions due to age and arteriosclerosis, or to some pre-existing source of myocarditis such as rheumatic fever and, in the case of cardiac hypertrophy, to the influence of hypertension. In diabetes, the most effective proof that this endocrine disturbance induces or is accompanied by arteriosclerosis is its presence in diabetic children and young adults. Likewise the most reliable estimate of the effect of hyperthyroidism on the cardiac anatomy could only be made by a study of cases in the early years of life previous to the onset of degenerative changes and unchanged by infectious disease. But such a group is difficult to find today. This series includes only 1 patient (Case 4, twenty-two years of age) definitely below the arteriosclerotic age.

The opinions at large on the cardiac pathology in hyperthyroidism are diverse. There is the opinion:

1. Once generally held and based on clinical rather than pathologic observations that the cardiac damage must be fairly severe, exemplified by the statement that "in most cases (of exophthalmic goiter) the exophthalmos and grave cardiac disorder cannot be relieved by treatment."[18]

2. That toxic necrosis in the myocardium may be present directly from toxic thyroid secretion; or indirectly, that the increased work, demanded from the heart, results in dilatation, then hypertrophy, and renders the heart more susceptible to secondary noxious influences.[19]

3. That moderate hypertrophy and dilatation are present with fatty degeneration, some interstitial myocarditis with fibrosis and lymphocytic infiltration.

4. Or, as is now generally held, that "with hyperthyroidism there is some evidence of focal degenerative lesions of the myocardium, but in most of these cases hypertrophy is about all that is found. The heart muscle, except for hypertrophy, is normal. There is no interstitial connective-tissue increase and no cellular infiltration. There is no valve lesion and no coronary disease."[20]

In this series, Cases 1, 2, and 3, presenting the most marked cardiac pathology, are in the arteriosclerotic age, have arteriosclerosis, coronary sclerosis, and a comparable degree of myocardial change. In Cases 1 and 3, dying clinically in a manner suggesting thyroid storm, death could be partly due to coronary sclerosis, independent of any thyroid factors. In Case 2, however, the repeated attacks of tachycardia and auricular fibrillation have undoubtedly been of serious import in the development of the auricular thromboses; but this influence may have accentuated, rather than caused the original formation of the thrombi, especially in the absence of a

TABLE I.—CLINICAL DATA.

Case No. Age. Sex.	Duration by		Thyroid activity by		Blood pressure.	Clinical diagnosis.	Response to iodin.	Antemortem course.
	Goiter.	Symptoms.	Symptoms.	Basal metabolic rate.				
1 X 45–F	16 yrs.	16 yrs.?	+++	+69	250/145	Endemic goiter, secondary hyperthyroidism; auricular fibrillation; hypertension; thyrocardiac	Good; fair risk	Scopolamin, morphin preoperative; fibrillation; apnea.
2 X 54–F	8 to 10 yrs.	8 to 10 yrs. marked 1 yr.	++++	None; comatose	120/70	Primary hyperthyroidism; auricular fibrillation; multiple arterial emboli; thyrocardiac	Prognosis poor on admission	Comatose on admission; cardiac failure; popliteal emboli; died fifth day.
3 59–F	17 yrs.	8 yrs.	+++	+36	160/70	Primary hyperthyroidism; auricular fibrillation; hypertensive heart disease, hypertrophy, (?) mitral disease; (?) thyrocardiac	Fair; fair risk	Fever; consolidation, right base; died third day.
4 22–F	5 yrs.	8 yrs.	++	+100	Normal (?)	Primary hyperthyroidism	Good; good risk	Restless, rapid pulse, second day; died third day.
5 40–F	3 yrs.	3½ yrs.	++++	None; too toxic	140/80	Primary hyperthyroidism; congestive heart failure; auricular fibrillation; thyrocardiac	Good; fair risk	Irregular, rapid pulse, cyanosis, coma, second day.
6 55–F	12 yrs.	2 yrs.	+++	+74	220/90	Endemic goiter, secondary hyperthyroidism; auricular fibrillation; hypertension; thyrocardiac	Good; fair risk	Postoperative cough, tracheitis; readmitted 2 mos. later, fever; died third day.
7 X 55–F	15 yrs.	1½ to 2 yrs.	+++?	None; semicomatose	140/80	Uremia; (?) thyroid crisis; bronchopneumonia; auricular fibrillation	Uremia, iodin given	Admitted semicomatose; nonprotein nitrogen 200 mg.; died 31 hours later.
8 54–F	4 yrs.	1½ yrs.	+++	+54	160/100	Endemic goiter, secondary hyperthyroidism; rheumatic heart disease, mitral stenosis; congestive failure; auricular fibrillation	Good; good risk	Five hours postoperative, cyanosis; recovered with oxygen; two hours later, cyanosis, death.
9 64–F	30 yrs.*	1 yr.	+++	+65	120/70	Endemic goiter; (?) thyrocardiac	Good; fair risk	Fifth day sudden decompensation; seventh day fibrillation; died ninth day.
10 50–F	35 yrs.	9 mos.	++	+49	158/72	Primary hyperthyroidism	Fair; good risk	Postoperative rapid pulse, fever, dyspnea; died third day.
11 40–F	4 mos.	4 mos.	++	+52	152/78	Primary hyperthyroidism	Good; good risk	Severe postoperative reaction; irregular pulse, died in postoperative storm, second day.
12 50–M	3 mos.	2 to 3 mos.	++	+50	140/80	Primary hyperthyroidism	Good; good risk	Postoperative rapid pulse, coma; died 20 hours later.

X = Nonoperative cases. * Operation 12 years ago, recurrence in 1 year.

marked degree of myocardial and coronary sclerosis. Case 8 is illustrative of the association of marked hyperthyroidism and cardiac failure, but with no cardiovascular changes at necropsy.

The aortæ in this series have no other changes than are to be expected for the age group. Also, the kidneys can be considered to have changes consistant with age and arterial conditions.

In necropsy findings on 3 cases of exophthalmic goiter, Müller[2] reported brown atrophy, some left ventricular hypertrophy, and fat streaks in the heart. Simmonds[3] in the hearts from 8 cases and Pettavel[5] in the hearts from 4 cases of "Morbus Basedowii" found only minor changes, mostly slight fibrosis, which they considered of no definite significance. On the other hand, Fahr[7] concluded in 1916, from observations on 7 cases of "Kropfherz," 5 of Basedow's disease, 2 of colloid strumas, that overactivity of the thyroid has a definite toxic effect on the heart. In 2 cases of exophthalmic goiter, which he stressed, in young women aged twenty-one years, thymicolymphatic hyperplasia and degenerative myocardial changes were present. The remaining 5 cases had interstitial myocarditis; but they were in the arteriosclerotic age and had arteriosclerosis. In 1921 Fahr[8] reported finding some evidence of a toxic myocarditis even in cases of simple goiter.

In 2 nonoperative cases of hyperthyroidism with auricular fibrillation, in which "the cause of death was myocardial exhaustion," Goodpasture[10] found fairly large foci of acute necrosis in the myocardium. Later, he observed the effect of large doses of thyroid gland and thyroxin upon the myocardium of rabbits; the animals showed characteristic clinical symptoms with definite but relatively slight myocardial lesions at necropsy.[11]

Wilson[12] reported the cardiac changes in 21 necropsy cases of exophthalmic goiter and toxic adenomatous goiter. The majority of hearts showed some degree of hypertrophy and dilatation, swollen fibers, and fatty changes; in only 2 was fibrosis noted grossly. The majority of the patients had been over forty years of age. Means and Richardson[21] summarize the necropsy findings on 12 cases (11 females, 1 male) with exophthalmic goiter, all that occurred among 5000 necropsies over a thirty-year period at the Massachusetts General Hospital; the hearts showed little hypertrophy, and arteriosclerosis when present was compatible with the age.

Thymus and Lymphatic System. The 2 cases of thymicolymphatic hyperplasia are outlined in the tables. In each, death was presumably associated with status thymicolymphaticus, especially since the hearts, lungs, and kidneys present no anatomic changes.

The association of thymic hyperplasia in hyperthyroidism was one of the constant features in the pre-iodin pathologic findings. Observations,[4, 6, 22] mostly from 1905 to 1915, reported some degree of thymic hyperplasia in 75 to 82 per cent of cases of exophthalmic goiter, even to 95 per cent of postoperative deaths. In one series,[9] thymic hyperplasia was present in all 37 necropsies of cases with

X = Nonoperative cases. * Operation 12 years ago, recurrence in 1 year.

TABLE II.—ANATOMIC DATA.

Case No.	Anatomic cause of death.	Thyroid.	Heart.*				Aorta.	Thymus.	Lymphatic system.	Spleen.	Pancreas.	Adrenals.
			Weight, gm.	Coronary arteries.	Valves.	Myocardium.						
1 X	Chronic myocarditis, (?) arteriosclerotic	Endemic goiter	500	S+++	0	S+ H++	S+++	0	0	Infarction, chronic passive congestion	0	0
2 X	Auricular thromboses; infarction of lung, liver, spleen	Primary hyperplasia, early involution	315	S+	0	S+ Auricular thrombosis	S+	0	0	0 105 gm.	0 80 gm.	0
3	Chronic vascular myocarditis; bronchopneumonia (early); (?) thyroid storm	Multiple adenomata, secondary hyperplasia	420	S++	Mitral thickened, (?) rheumatic	S++	S++	0	0	Congestion 240 gm.	Fibrosis +	Congestion.
4	Bronchopneumonia; acute bronchitis	Primary hyperplasia, early involution	340	0	0	0	0	0	0	Congestion 235 gm.	0	Congestion.
5	Postoperative storm; status thymicolymphaticus hyperplasia	Primary hyperplasia, late involution	350	0	0	S 0 Slight toxic myocarditis	0	Hy+++ 45 gm.	Hy++ (mesenteric and intestinal)	Lymphoid hyperplasia 225 gm.	0	0
6	Bronchopneumonia; pulmonary edema	Primary hyperplasia, moderate involution	360	0	0	0	S+	0	0	Congestion 250 gm.	0	0
7 X	Subacute glomerular nephritis; bronchopneumonia	Endemic goiter	350	0	0	S+ (? rheumatic)	S±	0	0	Congestion 225 gm.	0	Hy+
8	Hemorrhage into mediastinum, postoperative	Primary hyperplasia, moderate involution	300	0	0	0	0	0	0	Congestion 260 gm.	Fat +	0
9	Aortic stenosis; chronic myocarditis, (?) rheumatic	Endemic goiter	510	0	Aortic stenosis	S+ H++	S+	0	0	Chronic passive congestion 190 gm.	0	0
10	Bronchopneumonia, inhalation type; intrathoracic hematoma	Endemic goiter, secondary hyperplasia	230	0	0	0	0	0	0	0 180 gm.	0	Hy+
11	Bronchopneumonia, inhalation type; postoperative sepsis of thyroid	Primary hyperplasia, moderate involution	350	0	0	0	0	0	0 (Acute cervical adenitis)	0 Normal	0	0
12	Postoperative storm; status thymicolymphaticus hyperplasia	Primary hyperplasia, irregular involution	260	0	0	0	0	Hy+++ 40 gm.	Hy++ and congestion general	0 130 gm.	0 70 gm.	0

* S = sclerosis; H = hypertrophy; Hy = hyperplasia; 0 = negative.

active exophthalmic goiter dying before forty and 17 of 36 cases dying after forty years of age, or a total of 73 per cent of 74 cases. In the series at the Massachusetts General Hospital, a persistent thymus was noted in 9 of 12 necropsy records, weighing from 4 to 90 gm., and in 4 of the 9 there was enlargement of the spleen and lymph nodes compatible with status thymicolymphaticus. To 1919, Eddy[23] found in the literature 240 case reports mentioning the thymus in thyroid disease; the thymus was enlarged or persistent in 201, or 83 per cent.

Thymicolymphatic hyperplasia may, however, occur more frequently in cases of sudden death than usually considered. Of 2000 autopsied soldiers killed in action, Borst and Grace (quoted by Sternberg[24]) found lymphatic hyperplasia in 56 per cent, of which 86 per cent were nineteen to twenty years of age. Of 303 fatal cases of influenza over twenty-five years of age, Yamanoi[25] found evidence of persisting thymus in 26 per cent of 187 men and 20 per cent of 116 women.

Pancreas. The association of the pancreas and thyroid has been studied anatomically and physiologically. Joslin and Lahey,[26] in a thorough review of the subject of hyperthyroidism and diabetes, cite the various reports on anatomic changes. By feeding thyroid to animals, hypertrophy of the pancreatic islands has developed (Kojima and Hoshimoto). From a study of 4 cases, Pettavel[5] claims pathologic change, especially in the islands. In Holst's 10 cases of hyperthyroidism and diabetes, the pancreas of 4 showed no change, of 6 the weight was reduced, or number of islands reduced, or structures altered.

From the study of their 75 cases of hyperthyroidism and diabetes, Joslin and Lahey conclude that hyperthyroidism alone is the factor that leads to temporary glycosuria after operation for thyroid conditions; that the course of diabetes in nontoxic thyroid patients is uninfluenced by thyroid disease or removal of goiter; that the hyperthyroid patients from physiologic, pathologic, and statistical evidence is somewhat more prone to diabetes mellitus than ordinary individuals. It was the association of exophthalmic goiter, glycosuria, and polyuria and the known influence of the medulla oblongata on carbohydrate metabolism that led Müller[2] to study particularly the nervous system at autopsy in his cases and to seek a possible localization of the cause of exophthalmic goiter in the medulla.

Summary. 1. In hyperthyroidism the anatomic changes in the heart and bloodvessels are mainly due to coronary sclerosis, arteriosclerosis, or old rheumatic fever.

2. Arteriosclerosis, coronary sclerosis, and myocardial fibrosis when present are compatible with the age and with each other.

3. Certain deaths, clinically resembling crisis or postoperative storm, can be ascribed, on pathologic examination, partly or largely to such causes as coronary sclerosis, myocardial failure, and early bronchopneumonia.

sclerosis; H = hypertrophy; Hy = hyperplasia; 0 = negative.

4. There are no significant anatomic changes in the spleen, liver, kidneys, pancreas, adrenals, and ovaries.

5. Compared with the pre-iodin period there are apparently fewer medical deaths, fewer cases of thyroid crisis and postoperative storm, and a lower incidence of thymicolymphatic hyperplasia.

6. Hyperthyroidism *per se* has no toxic influence or direct pathologic action on the heart, but indirectly it accelerates the development and progress of pathologic lesions from other sources by causing increased work for the heart, tachycardia, and fibrillation.

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THYROIDECTOMY FOR THYROTOXICOSIS IN OLDER PEOPLE.

Report of 200 Cases After the Fiftieth Year.

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One does not ordinarily think of thyrotoxicosis as occurring in older individuals. It seems to be generally agreed that the disease is essentially an affection of young and middle-aged adults, the

maximal incidence being between the fifteenth and fortieth years (Marine,[1] Hertzler,[2] Rienhoff[3]). Hertzler states, "The acutely toxic goiter (Graves' type) is most common in early and middle life. The secondary toxic type (adenomas) are most frequent near the fortieth year. Those occurring beyond the menopause are apt to be long standing goiters and are marked by pronounced cardiac symptoms." He quotes Sattler as stating that the most violently toxic forms predominate in the fourth decade. The true degenerative type is seen most often after the fiftieth year.

No critical analyses or studies have been made in thyrotoxic patients in the later decades of life. Buschan,[4] in 495 cases of hyperthyroidism, found 31 who were over fifty years of age (6.5 per cent). Howard[5] states, "At all events it is very rare after the fiftieth year, and when reported it has usually been in males." Because of the paucity of accurate data and because thyrotoxicosis appears to go unsuspected in older people, we have analyzed a consecutive series of 200 such patients fifty years and older, who were subjected to thyroidectomy.

These 200 cases occurred in a consecutive series of 1060 patients operated upon for toxic goiter (18.8 per cent). In other words, nearly one-fifth of the entire series consisted of patients fifty years of age or older. One hundred and fifteen (57.5 per cent) were between fifty and fifty-five years, 38 (19 per cent) between fifty-six and sixty years, 32 (16 per cent) between sixty-one and sixty-five, 12 (6 per cent) between sixty-six and seventy years and 3 (1.5 per cent) were over seventy-one years of age. Of the latter 3, 2 were seventy-six years of age and 1 was seventy-three years at the time of operation. The average age of the 200 cases was 56.6 years. There were 55 males and 145 females. This is somewhat below the usual proportion of women to men, which is usually given as 4 or 5 to 1.

The series comprised 133 cases (66.5 per cent) of so-called primary hyperthyroidism (hyperplastic thyroids) and 67 (33.5 per cent) cases of secondary hyperthyroidism (toxic adenoma). This is extremely interesting in view of the fact that the toxic nodular goiter is said to occur most frequently in later life while the primary hyperplastic type predominates in younger patients.

The period of duration of goiter varied from one month to fifty years. One hundred and nine patients were not aware of any thyroid enlargement; 4 were indefinite as to the exact duration; in the remaining cases in which definite data were obtainable, the average duration was 11.68 years.

The duration of symptoms varied from two weeks to thirty-two years, the average duration of the entire series being 23.2 months. In 44 cases, where there was some accuracy as to the knowledge of the interval between the appearance of the goiter and the onset of symptoms, the average interval was found to be 14.5 years. In

1 case the interval was fifty years. In 25 instances the goiter and symptoms appeared coincidently. In 1 case the symptoms preceded the appearance of the goiter by seven and a half years.

Study of the symptoms (subjective and objective) reveals some interesting facts. The outstanding symptoms were weight loss (84.5 per cent), tachycardia (73 per cent), nervousness (67.5 per cent), tremor (55.5 per cent), weakness (43 per cent), palpitation (41.5 per cent) and exophthalmos (29 per cent). Other less frequent and pronounced symptoms occurred as noted in Table I. The question of weight loss is extremely interesting. It was the preponderant finding in our series. The weight loss in some of our patients was unusual—1 patient lost 54 pounds in one month, another 40 pounds in one month, a third 45 pounds in five weeks, a fourth 90 pounds in seven months, a fifth patient, while in the hospital being prepared for operation, lost 7 pounds in eleven days. The average weight loss in 135 cases in which accurate data were obtainable was 31.2 pounds.

TABLE I.—SYMPTOMS ENCOUNTERED IN 200 CASES OF THYROTOXICOSIS IN PATIENTS OVER FIFTY YEARS OF AGE.

	Cases.	Per cent.		Cases.	Per cent.
Weight loss	169	84.5	Restlessness	10	5.0
Tachycardia	146	73.0	Diarrhea	9	4.5
Nervousness	135	67.5	Crying spells	9	4.5
Tremor	111	55.5	Extrasystoles	8	4.0
Weakness	86	43.0	Precordial distress	7	3.5
Left heart enlargement	85	42.5	Dizziness	6	3.0
Palpitation	83	41.5	Sleeplessness	5	2.5
Irritability	60	30.0	Psychoses	3	1.5
Bilateral exophthalmos	58	29.0	Systolic and diastolic murmurs	3	1.5
Dyspnea	44	22.0	Crises	2	1.0
Systolic blow	35	17.5	Dysphagia	2	1.0
Auricular fibrillation	30	15.0	Left exophthalmos	2	1.0
Heat intolerance and excessive perspiration	26	13.0	Right exophthalmos	1	0.5
Cardiac decompensation	24	12.0	Pigmentation	1	0.5
Polyphagia	14	7.0	Paroxysmal tachycardia	1	0.5
Right heart enlargement	12	6.0	Gallop rhythm	1	0.5
Nausea and vomiting	11	5.5	Diabetes	1	0.5
Fatigability	10	5.0	Pulsus bigeminus	1	0.5

Bilateral exophthalmos was noted in 58 cases (29 per cent); 3 cases exhibited unilateral exophthalmos—in 2 cases the left eye protruded and in 1 case the right eye was involved.

The problem of cardiac involvement in thyrotoxicosis has only within recent years received its merited attention. It is being emphasized more and more that thyrotoxicosis *per se* has no destructive action on the heart musculature, which can be distinguished either microscopically or by interpretation of clinical findings, except that which is due to continuous mechanical strain. Lahey[6] has recently stated that patients without previously existing heart damage, relieved of their intoxication by adequate thyroidectomy, subsequently exhibit no permanent damaging effects in the heart.

Cardiac decompensation associated with hyperthyroidism is due to the effect of the hyperthyroidism upon a previously damaged heart rather than the damaging effect of hyperthyroidism upon the heart. The relative infrequency with which cardiac complications occur in young people and their frequent appearance in patients in late middle and the later years of life, when sufficient time has elapsed to develop cardiac damage, lends weight to the probability of this assumption.

Hamilton[7] states that, in thyrocardiacs, systolic murmurs are not heard except in those cases in which a preëxisting heart damage is present. Auricular fibrillation is the most frequent cardiac abnormality. It occurred in established form in 85 per cent of 142 thyrocardiacs from the Lahey Clinic. The older the patient the greater the possibility of fibrillation; similarly, coincident or pre-existing cardiac damage predisposes to this phenomenon.

In our own series, the cardiac manifestations were distributed as follows: 73 per cent had tachycardia, 42.5 per cent showed left heart enlargement on physical examination, 41.5 per cent complained of palpitation; dyspnea was present in 22 per cent, a systolic blow at the apex in 17.5 per cent, while pre-operatively, 15 per cent had auricular fibrillation. Cardiac decompensation was noted in 12 per cent of the series; right heart enlargement, precordial distress, systolic and diastolic murmurs, paroxysmal tachycardia, gallop rhythm, and pulsus bigeminus were found in a smaller number of cases. Of the 85 cases with left heart enlargement, 25 showed persistence of the left ventricular hypertrophy after operation, all occurring in hearts which had been damaged.

The fibrillators form a most interesting group. Several years ago Richter[8] stated: "Cardiac decompensation and fibrillation may cause some delay in the preparation for operation; I recognize their seriousness, but I insist that fibrillation, particularly, must not be considered a contraindication for surgery. Nothing is to be hoped for in such cases in the presence of continuous thyrotoxicosis; nothing in surgery is more brilliant than their recovery after adequate thyroidectomy." In our series of 30 cases of auricular fibrillation, 27 were restored to normal rhythm, postoperatively. Blood pressure readings corroborated what has been well established regarding a somewhat higher than normal pulse pressure. In this series, the average systolic pressure was 160 mm. of mercury, the average diastolic 80 mm., the average pulse pressure being 80 mm.

Of particular interest are the inciting factors that often precipitate an explosive from a quiescent hyperthyroidism. It has been taught for many years that mental or physical trauma, often of trivial character suffices to bring about an active thyrotoxicosis. We noted such factors in 21 of our cases—5 appeared to be of psychic origin, 16 of physical origin. The latter included acute infections and surgical procedures and are tabulated in Table II.

TABLE II.—PRECIPITATING FACTORS IN 21 CASES OF THYROTOXICOSIS IN PATIENTS OVER FIFTY YEARS OF AGE.

	Cases.		Cases.
Influenza	5	Unusual mental stress	5
Nasal operation	1	Financial reverses, 1 case	
Cataract operation	1	Death in family, 4 cases	
Acute laryngitis	1	Peritonsillar abscess	1
Lobar pneumonia	1	Acute appendicitis	1
Acute sore throat	2	Tonsillectomy	1
Hemorrhoidectomy	1	Radiotherapy	1

Hyperthyroidism presents no more distressing symptom than exophthalmos. This phenomenon is usually a later development. The diagnosis of thyrotoxicosis nearly always can be made before the ocular changes become marked, and their disappearance may be hastened by the institution of early and adequate surgical treatment. Our series comprised 58 cases of bilateral exophthalmos and 3 cases of unilateral exophthalmos. All but 5 returned to normal. In 4 instances the lesion became more marked following operation. This unusual phenomenon has recently been the subject of a paper by Zimmerman,[9] who reported 7 cases of postoperative exophthalmos, 5 from this service.

Toxic goiter patients reach the surgeon by devious pathways. One-third of our series of patients had been treated medically over varying periods of time, in some instances amounting to several years, before coming to surgery. These therapeutic agents included the prolonged and indiscriminate use of iodin, radiotherapy, digitalis, thyroidectomized serum, thyroid extract and the various "rest cures." Medical management was apparently ineffective, and it was only after adequate thyroidectomy that these patients were restored to normal.

What accurate method have we for determining the degree of thyroid intoxication and on what do we base our evidence of cure? H. M. Richter has succinctly stated that the most accurate and at the same time the simplest measure of the thyroid drive is expressed in the phrase, "basal metabolic rate." Adequate metabolic studies permit us to gauge accurately the success or failure of thyroidectomy. All of our metabolic studies are carried out in our own laboratory or in the hospitals where these patients are operated upon. In some instances these reports are obtained from competent internists whose work is known to be reliable. In this series of 200 cases we were able to obtain accurate pre-operative basal metabolic rates in 199. In the remaining case we were unable to obtain an accurate reading because of extreme nervousness and poor coöperation. There were 591 pre-operative metabolic readings in the 199 patients, an average of 2.97 rate per patient. The average pre-operative basal rate was 41.6.

While it is a recognized fact that iodin has a distinct and bene-

ficial effect in the primary or hyperplastic goiter case, there is some controversy as to the degree of improvement obtained in the nodular type. Without exception we noted a definite response to iodin in every case, despite the fact that in 20 cases the metabolic rate increased with, however, distinct clinical improvement. Of these 20 cases, 14 were of the primary hyperplastic type while 6 were nodular goiters. We also noted 26 cases in which the preoperative use of iodin made no appreciable change in the basal rates; 14 were adenomatous goiters, the remaining 12 being hyperplastic thyroids.

Postoperative studies reveal the following: Of the 200 cases, we were unable to obtain metabolic studies in 25 patients—there were 6 deaths, 18 patients were unable to return for various reasons and we were unable to follow up 1 patient because of a serious mental aberration. Accurate metabolic rates were obtained in the remaining 175 cases, the total number of readings amounting to 511, an average of 2.8 rate per patient. The average postoperative basal rate was 1.1−.

In 4 of the 175 cases the postoperative readings were above 15, which we have arbitrarily chosen as the upper limit of normal. One of the 4 with a 21 rate has since died—this patient had well-marked cardiovascular-renal degeneration. A second patient has a 16, and while apparently relieved of her thyrotoxicosis, has long standing cardiac damage. In a third, one reading of 34 was obtained shortly after operation. Although clinically well she has repeatedly refused to be further studied. In the 2 preceding cases we were unable to obtain basal readings. A fourth patient with a reading of 28 is distinctly toxic, but refuses to coöperate. Thus, of 175 patients accurately studied postoperatively, 171 (97.7 per cent) have been completely relieved of their thyrotoxicosis as measured by a return to normal of the basal metabolic rate.

A few words concerning the postoperative phenomena are pertinent: 64 patients presented evidence of varying degrees of hypothyroidism which lasted from a few weeks to six or eight months. All responded well to adequate doses of desiccated thyroid substance. There were 5 cases of mild temporary tetany. Eight patients showed some evidence of recurrent laryngeal nerve trauma: 6 of these were temporary, eventually returning to normal; 2 have persisted. In no instance was there injury to both nerves.

We have included in this series, 7 so-called recurrent cases: 4 of these had been operated upon elsewhere, 3 on this service. The 3 latter, who were accurately studied, did not at any time have a normal basal metabolic rate after the first operation. The 4 patients operated upon elsewhere had no clinical evidence of relief from their hyperthyroidism. These cases do not represent relapses; they are cases of persistent hyperthyroidism, unrelieved because of inadequate surgery. In every instance reoperation resulted in a return to normal of the basal metabolic rate.

There have been 6 deaths in this series of 200 cases. One death occurred in the remaining 860 cases which comprised this series. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent.

Summary. 1. A consecutive series of 200 cases of thyrotoxicosis is reported, for which thyroidectomy had been performed on patients varying in age from fifty to seventy-six years. These formed 18.8 per cent of a consecutive series of 1060 patients.

2. The proportion of females to males was 2.5 to 1.

3. Sixty-six and a half per cent of the cases were primary hyperplastic thyroids, the remainder were nodular goiters.

4. The average duration of goiter was 11.68 years; the average duration of symptoms was 23.2 months; the average interval between the appearance of the goiter and that of symptoms was 14.5 years.

5. The outstanding symptoms in this series were weight loss, tachycardia, nervousness, tremor, weakness, palpitation and exophthalmos, in the order given.

6. There were 30 cases of pre-operative auricular fibrillation, 27 of whom were restored to normal rhythm.

7. Sixty-one cases exhibited exophthalmos. All but 5 returned to normal.

8. The average pre-operative basal metabolic rate was 41.6 per cent above normal; the average postoperative rate was 1.1 −.

9. All of the cases, whether of the hyperplastic or adenomatous type showed a definite response to iodin therapy pre-operatively.

10. Of 175 patients upon whom accurate postoperative data are available, 171 were completely relieved of their thyrotoxicosis, as measured by a fall to normal of the basal metabolic rate.

11. There were 6 operative deaths in this series of 200 cases. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent.

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POSTOPERATIVE PARATHYROID INSUFFICIENCY.*

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POSTOPERATIVE parathyroid insufficiency is a syndrome characterized by a decrease in the serum calcium accompanied by irregular, intermittent attacks of tetany and in the later stages constitutional changes, trophic in nature. It is due to surgical extirpation or trauma of the parathyroid glands which results in more or less complete cessation of their functional activity. It may occur when a standard operative technique is used and therefore is often unavoidable.

On account of the rarity of this syndrome it is difficult to obtain a sufficient number of cases for observation both of the symptoms and the effect of different methods of treatment. During the last six years, 1924 to 1929 inclusive, at The Mayo Clinic, thyroidectomy was performed approximately 13,300 times. The ratio of female to male patients in the series was approximately 3 to 1. Parathyroid insufficiency was not noted in a male patient in the series, but in the last month we found the condition in a man. During this period, including the patients coming to the Clinic following an operation elsewhere, there were 88 cases of postoperative parathyroid insufficiency in female patients; the insufficiency was apparently transient and of short duration in half of the cases. Although 44 cases developed into the chronic and apparently permanent stage, only 6 of them could be considered as severe or complete insufficiency. In 21 of the cases the goiter was recurrent; probably this increased incidence was a result of anatomic displacement or injury to some of the parathyroid glands by the first or second thyroidectomy.

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Acute Stage. If the parathyroid glands are situated farther anteriorly than usual they may be more or less completely removed at operation, with resulting permanent insufficiency, or they may be temporarily injured so that for a time their function is decreased. As a result the concentration of calcium in the blood serum drops from its normal of 10 mg. for each 100 cc., producing abnormal irritability of the neuromuscular mechanism, characteristically demonstrable by tapping the facial nerve as it emerges from beneath the parotid gland which causes the muscles of the lips and mouth to twitch (Chvostek's sign). This sign usually becomes positive on the first or second day after operation as soon as there is a decrease in the serum calcium of 2 mg. for each 100 cc. However, Chvostek's sign is sometimes present in normal persons. Further decrease in serum calcium leads to a characteristic spasmodic contraction of the muscles of the forearm, less frequently of the calf of the leg and occasionally of other groups of muscles; this tendency to tetany can usually be demonstrated before the contractions become spontaneous by constriction of the arm (Trousseau's sign) which will often initiate the characteristic contraction of the forearm. Spasm of the ocular muscles with difficulty in accommodation is not uncommon. Another important group of muscles that may be affected are the adductor muscles of the vocal cords causing laryngeal spasm and the secondary symptoms of respiratory obstruction. Those muscles are supplied through the recurrent laryngeal nerve, and the trauma incident to operation, which is not necessarily permanent, may act as an irritant of this neuromuscular system possibly in a manner somewhat similar to the phenomena obtained by tapping the facial nerve. In fact, laryngeal spasm may be one of the first tetanic signs of parathyroid insufficiency, although it is not likely to occur unless associated with some trauma to at least one of the recurrent laryngeal nerves as revealed by laryngoscopic examination. In certain persons actual spasm of muscle is a rather late phenomenon and the serum calcium may have decreased to 7 or 6 mg. before tetany appears on the third, fourth or fifth day; however, such patients usually complain of previous periods of numbness and tingling of the fingers which may often pass unnoticed for several days, especially if the patient is of the phlegmatic and uncomplaining type. On the other hand, if the patient is of the nervous type and easily frightened, these sensations are usually mentioned quite early and in such a manner as to suggest hysteria. There is experimental as well as clinical evidence to suggest that the spasms are more likely to occur and to be severe when the serum calcium is falling rapidly than when it is falling gradually or after it becomes constant at a low level.

Approximately half the cases in which symptoms of parathyroid insufficiency are exhibited are temporary and never pass over to the chronic stage; therefore it is evident that simple therapeutic measures

will often be sufficient. Aub, Bauer, Heath and Ropes have shown that if patients with hyperthyroidism are on low calcium intake, there is a definite tendency to a larger negative calcium balance than that found in normal persons. Therefore, the readily available stores of calcium may be used up during the course of the hyperthyroidism and may be further acutely depleted during the first day or two of the postoperative reaction. Consequently temporary interference with the function of the parathyroid glands might readily cause, for a short time, a drop in the blood calcium with the accompanying phenomenon of neuromuscular irritability.

The therapeutic problem involved in the immediate postoperative treatment of the acute stage of parathyroid insufficiency is, of course, to hold in check the tetanic symptoms until all immediate danger from the operation is over. For this purpose the administration of calcium lactate by mouth is usually sufficient if it is given in generous teaspoonful doses (approximately 30 gr.) dissolved in water every two or three hours after the symptoms are first observed. If there is difficulty in swallowing, six additional teaspoonfuls of calcium lactate can be dissolved and given by proctoclysis. The calcium lactate should be thoroughly dissolved in a convenient quantity of water; apparently it is not as effective when dry or in an emulsion; it seems to be nearly valueless if given in tablets. The intravenous administration of calcium chlorid will also immediately relieve the tetany; however, even if the attacks are very severe, a beneficial effect can usually be obtained almost as quickly if calcium lactate is given by mouth every fifteen minutes or every half hour until three or four doses have been administered. It has proved more satisfactory to give the calcium by mouth frequently and regularly whenever possible, since repeated intravenous administration is undesirable, especially in this instance, because of danger of a superficial slough if some of the calcium chlorid is accidentally introduced into the subcutaneous tissues; also thrombosis of the veins usually occurs, making the intravenous method progressively more difficult. It is rarely necessary to use parathormone in the immediate postoperative treatment and we have found it advisable not to use it until we are certain that we are dealing with the persistent or chronic form of parathyroid insufficiency.

As soon as the patient is out of operative danger, then the administration of calcium (and of parathormone if it has been started) should be stopped so that the true condition of affairs can be determined while the patient is still under observation in the hospital. It is, of course, unfortunate if the calcium and the parathormone are continued until the patient leaves the hospital, apparently in good condition, and then with cessation of medication to find that the symptoms of parathyroid insufficiency are developing. Under such circumstances the condition of the patient is likely to become serious rapidly; consequently it is advisable to hold him under

supervision until it is known whether the condition becomes chronic as a result of permanent insufficiency of the parathyroid glands.

Chronic Stage. We shall consider in this paper particularly the diagnosis and treatment of the chronic stage, which is an apparently permanent form of parathyroid insufficiency. After the condition has become chronic, there may be a partial physiologic adjustment to the lowered serum calcium in that the tendency to definite muscular cramps or spasms may be decreased, although there is often more pronounced muscular weakness and fatigability. In extreme conditions there may be marked hypertonicity of the extremities, malleable in type. The muscles of the heart may be involved in the weakness which results in the late stages in cardiac dilatation, insufficiency and the attendant phenomena if there is a coincident organic cardiac lesion. Spasm of the ocular muscles with disturbance of accommodation may cause difficulty in reading. There is an increase in mental and nervous irritability. The patient looks bad, and the face is pasty and masklike, with edema sometimes suggesting the edema of myxedema. The basal metabolic rate, however, instead of being decreased, may be elevated (a fact we have observed both in human beings and in dogs), although a rate as low as −20 may be encountered without an existing thyroid insufficiency. If the condition has persisted for a long time and the treatment has been insufficient, trophic changes develop, such as the formation of cataracts, softening of the teeth and loss of hair. Occasionally symptoms are present which can be referred to gastrointestinal irritability. The serum calcium may range between 5 and 7 mg., and in the milder cases around 8 mg. for each 100 cc.

Thyroid insufficiency (myxedema) may be simultaneously present with parathyroid insufficiency. However, we have as yet not encountered such a case; it is only likely to occur after absolutely complete thyroparathyroidectomy for malignant disease. If there is thyroid insufficiency the symptoms due to each condition must be sharply differentiated in order that the appropriate and independent treatment for each disease can be carried out.

The severity of the symptoms of chronic parathyroid insufficiency may depend on whether the function of the glands is completely or only partially interfered with or it may depend on a difference in the reaction of the individual, or more probably, it may depend on both factors. Considerable evidence is available which shows that the susceptibility of individuals varies and also that age and sex are factors. That sex is a factor is indicated by the rarity of cases reported in men. If it does occur in the male it is probably mild as in the case observed by us, which although chronic, was easily controlled by calcium lactate and cod-liver oil without parathormone. Whether the infrequency of occurrence in men is due to the slightly different anatomic site of the parathyroid glands or whether

men are less sensitive to their removal is not known. The apparent infrequency, however, is far greater than can be accounted for by the lower incidence of thyroid disease and thyroidectomy in men. It is also well known that complete thyroparathyroidectomy is more dangerous to young than to older animals. That individuals, possibly as a result of temperament, are affected differently by removal of the parathyroid glands is indicated by the experiments of Hammett, who found that in a series of tamed rats only 12 per cent died from the tetany of parathyroid insufficiency within forty-eight hours after thyroparathyroidectomy, whereas 79 per cent of ordinary albino rats, and 90 per cent of pugnacious caged wild Norway rats died.

It may be assumed that the acute stage of postoperative parathyroid insufficiency has passed into the chronic stage if, at the end of ten days or two weeks after operation, cessation of calcium medication allows the symptoms to recur and persist; it is necessary, however, to be certain of this by repeated occurrence of the characteristic spasms of the muscles and either a further drop or a continuance of a low serum calcium. At this time the patient is out of operative danger so that a permanent form of treatment need not be instituted before it is known that it will be necessary and, further, an attempt should be made to keep the dose as small as possible and not to give parathormone until it is proved to be necessary.

After the chronic nature of the condition has been established we first give calcium lactate four or five times a day together with two teaspoonfuls of cod-liver oil or 10 drops of irradiated ergosterol once daily, hoping thus to maintain the patient relatively free of symptoms and with a serum calcium not lower than 8 mg., or possibly, 7.5 mg. for each 100 cc. It is advisable to observe the patient on this regimen if possible for several weeks, provided there are not actual cramps of the muscles, as the milder forms may not require parathormone, in some instances probably because there is some functioning parathyroid tissue available. Both on account of the cost of parathormone and the trouble of administration, its use should be avoided if the patient does well on calcium lactate and cod-liver oil or ergosterol; it is even permissible to allow in some instances a slight tingling, or formication of the skin, and a positive Chvostek sign. If, however, on this regimen the patient becomes more irritable, does not regain strength and is easily fatigued, and if at the same time there is a peculiar pasty or edematous look suggesting possibly myxedema without, however, a lowered metabolic rate (in fact the rate may be elevated unless actually associated with coincident insufficiency of the thyroid gland), and if there is a tendency for the blood calcium definitely and persistently to remain below 8 mg., and especially if it falls below 7 mg., treatment by glandular substitution should be instituted by the regular administration of parathormone. Except in old neglected cases, para-

thormone should be administered before sufficient time has elapsed for the development of trophic changes.

In our use of parathormone in chronic and apparently permanent parathyroid insufficiency we have been guided by the principles which took such a long time to learn in the treatment of thyroid deficiency (myxedema), namely, that the dose administered must be maintained probably indefinitely, that it must be given at regular intervals, and that it should be given in the minimal dose needed to keep the patient in good condition. In treatment by glandular substitution it must be remembered that the favorable effects of the correct dose are not immediately manifest nor on the other hand are the unfavorable effects of an improper dose immediately recognizable; changes in the dose, therefore, must be small and at rather infrequent intervals. We believe it essential for the proper treatment of parathyroid insufficiency that an attempt be made to give regularly the quantity of parathormone equivalent to the daily secretion of the parathyroid glands. However, we do not have a method of determining what this quantity is nor of measuring the response of the treatment in parathyroid insufficiency as we have with the measurement of thyroid insufficiency and medication, by means of the basal metabolic rate. In fact, in parathyroid insufficiency we must be guided to a large extent by clinical evidence. However, frequent observations of the level of the serum calcium are a valuable means of estimating the efficiency of the treatment, provided it is remembered that it is an indirect measurement which is influenced by many factors and that in the presence of a normal or nearly normal concentration of calcium these factors are more or less controlled. Woodyatt has just emphasized the fact that a deduction diametrically opposite to the actual fact may be made from observations on the concentration of the blood, using glucose curves as examples.

We do not as yet know what part of the mechanism is disturbed by removal of the parathyroid glands. However, we do know, as originally shown by Collip, that parathormone in large doses, especially if frequently repeated for a short time, results in an elevation of the serum calcium even in normal individuals and that if pushed to excess will kill dogs. Aub and his associates have shown clearly that the administration of parathormone in large doses causes increased elimination of calcium in human beings, as previously shown by Greenwald and Gross for dogs. It is obvious that we do not desire to increase the elimination of calcium by the administration of large doses. The following case is illustrative of: (1) The immediate postoperative control of the symptoms by calcium lactate which, however, proved only temporary; (2) the good effect of moderate doses of parathormone with the simultaneous administration of calcium lactate and cod-liver oil; (3) the harmful effect of giving too large doses

of parathormone and the recognition of this fact, and (4) the excellent effect obtained by the constant and regular administration of small doses of parathormone in conjunction with calcium and cod-liver oil. Furthermore, after two and a half years an unsuccessful attempt to stop the administration of parathormone was made both in the hope that its use might not be indefinitely necessary and to be sure that we were actually dealing with a severe case of chronic parathyroid insufficiency. As the history of the case illustrates nearly all the essential points, it is presented in considerable detail.

Case Reports.—Case I. An unmarried woman, aged twenty-six years, first came to the Clinic in January, 1925. At that time a definite diagnosis of exophthalmic goiter could not be made, as the patient had been taking compound solution of iodin (Lugol's solution) and there was a possibility that the condition was nothing more than neurosis, especially as she had always complained of being nervous and there was a family history of psychosis. The basal metabolic rate was only +13. She was not seen again until November 4, at which time there was no doubt of the presence of exophthalmic goiter; the basal metabolic rate was +87; this decreased to +38 with the administration of the iodin.

Thyroidectomy was performed November 23, 1925. The postoperative reaction was not severe and the patient did well until the fifth day after operation when she complained of mild cramps; these rapidly became worse, resulting in definite carpal spasm. The serum calcium had fallen to 4.9 mg. and the inorganic phosphate had risen to 5.4 mg. for each 100 cc. Although notes had not been made on the history it is certain that inquiries would have elicited numbness and tingling of the fingers earlier, probably after the serum calcium had decreased to 8 mg. Teaspoonful doses of calcium lactate were given four times the first day symptoms were noted, eight times the next day, eleven times the next and then reduced to and continued at four times daily. The patient improved rapidly for the first few days on the larger doses of calcium, but after the dose was reduced to four times daily the prickling sensation gradually returned and was again definite on the ninth day after operation; tetany recurred on the tenth day. The serum calcium fluctuated between 4.9 and 5.8 mg. In addition to a teaspoonful of calcium lactate four times daily parathormone was started first by mouth, 25 units twice daily for two days, and then three times daily for four more days, after which the oral method of administration was abandoned. As the patient had severe tetany on the day after parathormone was given by mouth, an additional 25 units were given subcutaneously every other day with an increase in serum calcium to 6.8 mg.; this was accompanied by general improvement and the disappearance of tetany. In order to attempt to elevate the calcium to normal, as other observers have done, we increased the subcutaneous dose of parathormone to 25 and then to 30 units twice daily, the calcium lactate of course being continued. Also cod-liver oil was given three times daily, before meals. On this regimen the serum calcium increased to 7.1 mg. by December 14; then the parathormone was reduced to 50 units once daily and the serum calcium increased to 9.5 mg. and the phosphate decreased to 3.7 mg. The patient was in excellent condition, with no tetany and a practically negative Chvostek sign. She went home December 23, with instructions to maintain that dosage. March 22, 1926, she was doing so well that she thought it might be possible to reduce the amount of parathormone; this she did although not under our immediate supervision.

With the reduction in parathormone to 25 units daily the symptoms of parathyroid insufficiency, especially the tingling sensation and twitching of the facial muscles and an occasional carpal spasm, returned. It is possible that the patient likewise reduced the calcium lactate and omitted the cod-liver oil. The patient became frightened on the return of symptoms and in consequence took 50 units of parathormone for two days, then 100 units for three days and finally 150 units on the day before she returned to the Clinic; probably she did not take much calcium lactate. Subsequent experience has shown that for a short time symptoms increased whenever a sharp reduction is made in too high a dose of parathormone but after a short time the patients again become adjusted to the smaller dosage and are nearly, if not completely, free of symptoms and tetany, provided the calcium was continued and the dose of parathormone was not too greatly reduced; small changes are better than big changes.

When the patient reached the Clinic, following the repeated large doses of parathormone, she was nervous, irritable, worried and frightened; she did not look well and there was a peculiar pastiness and puffiness of the face. Chvostek's sign was positive. She complained much of a tingling sensation and numbness, but an actual carpal spasm was not present. Our first thought was the possibility of an overdosage of parathormone and we reduced the dosage to 25 units daily, making sure that she was taking 5 teaspoonfuls of calcium lactate regularly. Blood was immediately taken for calcium determinations but when the report was made, much to our surprise, instead of being high the calcium was 6.7 mg. and the inorganic phosphate 4 mg. and on the following day, 5.3 mg. and 3.9 mg. respectively. However, the patient was improving and by the sixth day was much better both objectively and subjectively with less tingling and no spasm, and the Chvostek sign was only slightly positive although the condition of the blood remained the same. From then on the patient's condition improved rapidly on 25 units of parathormone a day with 5 teaspoonfuls of calcium lactate and 3 teaspoonfuls of cod-liver oil. After eight days the serum calcium had increased slightly to 6.1 mg. and the inorganic phosphate had decreased to 3.4 mg. Both physically and mentally the patient's condition was excellent. The parathormone was consequently reduced to 20 units daily and April 27, the serum calcium having increased to 7.1 mg., the patient was allowed to go home with instructions to continue taking 20 units of parathormone, 5 teaspoonfuls of calcium lactate dissolved in water and 1 teaspoonful of cod-liver oil daily. Care was taken to impress on her the necessity of regularity and faithfulness in taking the medicine.

The patient returned September 29 in good condition mentally and with good strength. She was leading a nearly normal life which was in marked contrast to her condition at her previous return when she was so sick from overdosage of parathormone. However, she had a positive Chvostek sign and tingling of the lips but no muscular spasm. The blood calcium was about the same as when she left, 6.9 mg., and the inorganic phosphate was 3.8 mg.

It seemed likely that the dosage of parathormone was still too high and in consequence it was halved to 20 units every other day, with the development for a few days only of some of the milder symptoms. October 7 (ten days later) the patient was allowed to go home on this dosage and was also instructed to continue 1 teaspoonful of calcium lactate five times daily and 1 teaspoonful of cod-liver oil daily. For the next four months she continued on this medication and returned February 16, 1927, in excellent condition. As three determinations of serum calcium showed 7.1, 8 and 8.1 mg. for each 100 cc. and inorganic phosphate of 3.3 mg., the treatment was not changed.

The patient's next return was September 19, 1927. She was very well; the serum calcium was 8.1 mg. and the inorganic phosphate 3.7 mg. The

dosage of parathormone was reduced from 20 units to 10 units every other day, and the calcium lactate was maintained at 1 teaspoonful five times daily. This reduction in dose caused the development of slight symptoms; the chief complaint during the period of readjustment was slight dizziness and considerable formication of the skin; as she expressed it, her face felt as if a million ants were crawling over it. Therefore, on October 12, the parathormone was increased to 15 units every other day with the same amount of calcium and cod-liver oil; on this treatment the patient went home and did well. She returned in January, 1928, in excellent condition in every way with blood calcium of 9.2 mg. and inorganic phosphate of 4.2 mg. The dosage of parathormone was not changed but the calcium lactate was reduced to 1 teaspoonful three times daily. On this medication during the spring and summer at home she continued to do well. When she returned in July, 1928, her physical condition was excellent; the serum calcium on the lower dosage of 15 units every other day had increased to 9.6 mg. and the inorganic phosphate had decreased to 3.6 mg. Her mental attitude, however, was not so good, apparently, because she was disappointed at not going into a convent. On July 27, the parathormone was reduced without difficulty to 10 units every other day and the calcium lactate was continued at 1 teaspoonful three times daily; cod-liver oil was likewise continued in doses of a teaspoonful once daily. This regimen was continued after the patient went home and for the following three and a half months her condition was excellent.

The patient returned in November, 1928, without any complaint whatsoever. Roentgenograms of the hands did not reveal rarefaction of the bones. The serum calcium was 10.3 mg. and the inorganic phosphate was 4.7 mg. At her urgent request an attempt was made to stop the parathormone but the calcium lactate and cod-liver oil were continued. It seemed wise at this time to ascertain again whether the parathyroid insufficiency still persisted as there was a possibility that either regeneration of parathyroid tissue had occurred or a compensating mechanism had developed which would render the use of parathormone unnecessary.

On December 1, the fourth day after the parathormone had been stopped, the patient did not look so well. There was slight puffiness of the face and Chvostek's sign had become definitely positive. The serum calcium had fallen to 8.5 mg. and the inorganic phosphate had risen to 6.6 mg. Ten units of parathormone were given and similar doses were given on December 7 and December 10. During this period the patient had a moderate attack of influenza with a temperature of between 102° and 103° F. and was in bed for several days. Although on December 18, the ninth day after the last dose of parathormone, the serum calcium was still 8.9 mg. and the inorganic phospate 4.3 mg., her general appearance was not good and her face reminded one of myxedema. Her mental condition was not good; she was extremely nervous, although spasms were not present. The Chvostek sign was not materially different. She was allowed to go home on 5 units of parathormone twice a week, 1 teaspoonful calcium lactate three times daily and a teaspoonful of cod-liver oil. The day the patient was dismissed from observation a note was made as follows: "Don't like her looks; probably will have to increase the dose of parathormone. Her face suggests chronic parathyroid insufficiency something like myxedema." (We had had one other case in which the facial expression suggested myxedema and we anticipated a low basal metabolic rate; the rate, however, was above normal and the serum calcium was low, and improvement had rapidly followed treatment of parathyroid insufficiency.) Within a few days the patient wrote a most discouraging letter in which she complained that she was dizzy, that she could not see well and that she could not get around as she had before; her vision apparently was disturbed by spasm

of the ocular muscles, thus causing difficulty in accommodation. Her hands shook so that she could not inject the parathormone herself. On her own initiative she returned first to 5 units daily for two days, then to 20 units every other day for four days and then back to 10 units every other day, that is, to the dosage on which she had previously done so well.

The patient returned January 21, 1929; her condition was much better than after she got home on the low dosage of 5 units twice weekly and even better than when she left the Clinic to go home, although not nearly as good as before the attempt was made to stop parathormone. The serum calcium, however, was 9.7 mg. and the inorganic phosphate was 5 mg. for each 100 cc. Several months passed before the patient regained what she lost during the period in which the attempt was made to stop the parathormone and before she was back into her former good condition. As the serum calcium was above normal, we allowed her to go home on 8 units every other day which, however, after two weeks she increased to 10 units; she continued taking 1 teaspoonful of calcium lactate three times daily and a teaspoonful of cod-liver oil. She maintained this regimen conscientiously and did so well that she did not return again for nearly a year although we received letters from her in regard to her condition almost every month. When she returned, December 26, 1929, she looked and felt well and had no significant complaints except slight cardiac arrhythmia. The serum calcium was 9.5 mg. and inorganic phosphate 4.7 mg. No alteration was made in medication and several letters since she went home indicate that she is continuing to do well (June, 1930).

This case illustrates the continuous treatment of severe parathyroid insufficiency over a period of more than four and a half years. However, every now and then such patients come under observation on whom thyroidectomy had been performed many years previously and before parathormone was available, and in fact while our knowledge of the subject was limited. In general, patients will have had more or less calcium and recently possibly intermittent doses of parathormone. After months or years, they usually cease to have definite cramps of muscles and there is apparently a partial adjustment of the neuromuscular system to a lowered calcium level. They are, however, extremely nervous and irritable, weak and semi-incapacitated. A laryngeal stridor may be the most distressing of their complaints and is often particularly objectionable when they are asleep by causing a loud crooning type of respiration, in part due to associated injury of the recurrent laryngeal nerve. As we have mentioned, we do not know whether the patients that survive, on insufficient treatment, although still maintaining evidence of parathyroid insufficiency, survive with only a partial abolishment of the function of the parathyroid glands or whether certain patients, especially older patients, are more resistant to some of the ill effects of the deficiency. We have seen several such patients; some patients improved on cod-liver oil and calcium lactate and others required parathormone also. The following case is an example of the latter group.

CASE II.—Thyroidectomy was performed on a woman, aged forty-seven years, in November, 1917. Four days after the operation definite parathy-

roid insufficiency developed; the tetany was controlled at the time by calcium. Later, as the condition became chronic a cramp-like sensation developed in the eyes which made her ataxic but not dizzy, and she was likely to fall. She was treated intermittently by calcium. In February, 1919, posterior gastroenterostomy was performed for duodenal ulcer, as shown by roentgenograms. In June, 1923, a combination of gastro-intestinal distress with chronic stasis in the ileum led to resection of 7.5 cm. of the ileum, appendix, cecum, ascending colon, hepatic flexure and two-thirds of the transverse colon. The next year an operation was performed for bunions. During all these years she was complaining of the symptoms of parathyroid insufficiency such as tingling of the hands and fingers, weakness, irritability and embarrassed respiration in part due to bilateral adductor paralysis. A test of the serum calcium was first obtained in October, 1922, when the values fluctuated between 6.5 and 7.7 mg. Calcium lactate in small doses was given at that time for a short period; also desiccated thyroid extract was tried in an arbitrary manner.

Regular treatment was instituted in August, 1927, by starting parathormone, 10 units every third day; in September calcium lactate was started, 1 teaspoonful dissolved in water four times daily. On this regimen the patient improved greatly and the serum calcium increased to normal. She underwent tonsillectomy and 2 operations for bilateral cataract (cataract is not an infrequent complication). In June, 1928, an attempt was made, lasting one and a half months, to discontinue the administration of parathormone; this, however, led, as in the previous case, to gradual return of her difficulty, with loss of strength, increasing pallor, greater nervousness and more frequent attacks of respiratory spasms. The serum calcium decreased from 9.6 to 7 mg. In October, 1928, parathormone, 10 units twice weekly, was again started and after a short time 10 units were given every other day. As a rule the patient was faithful about taking the calcium lactate but for a time she probably did not do so. Recently she has been in excellent health and her strength is very good. Tingling and cramps have disappeared. She breathes easily and comfortably and she has no inclination to fall. Her serum calcium is normal and she is now taking 10 units of parathormone every other day, 1 generous teaspoonful of calcium lactate four times daily and 1 teaspoonful of cod-liver oil daily. She is very much pleased with her present condition and is completely reconciled to the advantages obtained by taking the medicine regularly.

Comment. Since Dragstedt has recently reviewed in detail the experimental work on the physiology of the parathyroid glands it is unnecessary to do so here. The essential points brought out in his review and in the previous review of Boothby which concern the treatment of parathyroid insufficiency are that calcium lactate administered continuously and in sufficiently large doses will in a large proportion of cases afford permanent relief from the tetanic symptoms and usually permit the indefinite survival of dogs on which thyroidectomy has been performed;[15, 17, 18, 34] that ingested calcium lactate does not produce acidosis;[35] that the administration of cod-liver oil[30] might be beneficial in the treatment, and that the administration of parathormone would likewise relieve the symptoms of parathyroid insufficiency,[10] although the frequency of administration and the dosage had not then been worked out.

Since Dragstedt's review, Brougher and also Wade have presented further evidence that cod-liver oil increases the beneficial

effect of calcium lactate although Greenwald and Gross are still somewhat doubtful about this. However, that the administration in proper doses of vitamin D is a valuable aid in the treatment of parathyroid insufficiency is further supported by the experiments on the effect of irradiated ergosterol of Brougher and of Jones, Rappoport and Hodes. The latter investigators were able to produce hypercalcemia even in parathyroidectomized dogs by large doses of irradiated ergosterol and to keep them alive indefinitely and in apparently good health on repeated doses. Hess, Weinstock and Rivkin, however, were unable to produce hypercalcemia by its use in parathyroidectomized dogs and monkeys, although in normal animals they could readily do so. The previous experiments of Hess and Lewis, and of Urechia and Popoviciu, on the other hand, were negative. However, in view of the considerable evidence available indicating the beneficial effects of vitamin D in parathyroid deficiency it certainly seems advisable to incoporate the use of cod-liver oil or irradiated ergosterol in the treatment of this condition.

Higgins and Sheard, and Higgins, Foster and Sheard have shown that the parathyroid glands in the chick develop normally only in the presence of both the visible and ultraviolet portions of radiant energy and they concluded that hyperplasia of the parathyroid glands develops whenever a chick is denied vitamin D either in the radiant energy or in the diet. Swingle and Rhinhold had previously shown that irradiation causes startling improvement of the violent symptoms following parathyroidectomy in dogs. In this connection it is an interesting observation that in certain chronic cases patients are much better in the summer and early autumn months than in the winter or early spring, and in consequence we advise our patients to obtain as much sunlight as possible. In our experience, more cases of parathyroid insufficiency occurred in the months of January, February, March, October, November and December than occurred in the months of April, May, June, July, August or September, even though the greater number of operations occurred in the latter group of months.

Shortly after Collip's parathormone was available, Greenwald and Gross showed that the excretion of calcium in the urine, which was negligible before the administration of parathyroid extract, increased promptly on the administration of large doses and just as promptly decreased when it was stopped; the increase in the feces was not so great but continued for a longer time. Albright, Bauer, Ropes and Aub have confirmed this in their observation of human beings; their chief observations were that parathormone raises the serum calcium and gradually increases the excretion of calcium in the urine without affecting the fecal excretion and that after cessation of medication the excretion of calcium gradually falls to a level below that found before its administration. Parathormone caused

also an abrupt increase in the excretion of phosphorus and an abrupt fall to a level below that found in the control period. Large doses were used over relatively short periods and only the immediate effects of massive doses were studied as a case of parathyroid insufficiency was not available in which it might be necessary to use the parathormone continuously. Bauer, Albright and Aub have shown that the prolonged administration of parathormone to cats results in demonstrable decalcification of the bones.

Greenwald and Gross, in 1925, warned against the dangers of parathormone and stated that the hypercalcemia it produces is not due to improved assimilation but is the cause of increased loss of calcium. The observations of Greenwald and Gross, of Hunter and Aub, and of Albright, Bauer, Ropes and Aub, demonstrating increased excretion of calcium following the administration of large doses of parathormone, readily explain why larger and larger doses will increase the severity of the symptoms which are diminished by small doses and why in the early days of its use one was so easily led into overdosage.

The crucial points in the treatment of Case I are that, after recognizing the probability of overdosage of parathormone, we did not entirely stop parathormone but only reduced the dosage, and at the same time continued without interruption the administration of calcium lactate and cod-liver oil. The continuance of the administration of calcium lactate combined with the reduction in the dosage of parathormone resulted in such a marked improvement that the beneficial effect of the reduction could not be overlooked, and this procedure constituted the essential point of difference in the method of treatment from that used in the case recently reported by Lisser and Shepardson. These observers under similar conditions stopped the administration of both parathormone and calcium lactate and did not in consequence observe any marked improvement; furthermore they did not at any time make use of the assimilative effect of vitamin D by the administration of cod-liver oil.

The cases reported by Aub (later referred to by Hunter), by Kemper, Elmer and Scheps, Snell, and other clinicians are of too short duration or are presented with too little detail definitely to determine the effects of varying the dosage of parathormone, although in some of the cases there seems to be a suggestion of the better effect of small, regularly administered doses. Snell's patient is an example of the group of chronic cases, previously referred to, in which the condition is controlled by calcium and in which parathormone is not needed, although there is a suggestion that its temporary use helped to bring the patient more rapidly into a good condition.

Summary. In acute postoperative parathyroid insufficiency the tetanic spasms, including laryngeal spasm, can be controlled by

the administration of a generous teaspoonful of powdered calcium lactate dissolved in water every two hours. In the severe cases in which the patients have difficulty in swallowing, 5 or 6 additional teaspoonfuls of calcium lactate are dissolved and given by proctoclysis. Only rarely will it be necessary to give calcium chlorid intravenously. Also in the immediate postoperative period it will hardly ever be necessary to give parathormone.

In the milder cases of chronic postoperative parathyroid insufficiency (in some of which insufficiency probably is not complete) the condition can sometimes be controlled by the regular administration, four or five times a day, of 1 teaspoonful of calcium lactate dissolved in water, aided by the administration of 2 or 3 teaspoonfuls of cod-liver oil daily. Irradiated ergosterol can be used instead of cod-liver oil although as yet the dosage advisable for longer periods is not determined.

In the more severe cases, including those in which insufficiency apparently is complete, parathormone must also be administered. As in all deficiency diseases, medication must be continuous and regular, and in the presence of complete deficiency it must probably be administered indefinitely. It is known that a large single dose of the active principle of the thyroid glands which will not cause serious trouble, may, if maintained, cause marked hyperthyroidism, and if the dose is sufficiently large may prove fatal. It is pointed out similarly that the long-continued use of parathormone in large doses, which may be safe if used only for a short period, can be harmful if continued for a long period. In general, it has been found that for continuous administration only small doses should be used such as 5 units of parathormone daily, or 10 units every other day. Sometimes 10 units every day, and occasionally for short periods, 20 units daily will be needed; the use of larger doses over any considerable time is probably dangerous.

On a regimen of calcium lactate, cod-liver oil or irradiated ergosterol, such as has been outlined, even patients with severe and apparently complete parathyroid insufficiency can be maintained in good, if not perfect, health. If the parathyroid insufficiency is less severe and apparently not complete the patient can be maintained in good condition without parathormone if suitable doses of calcium lactate and cod-liver oil or irradiated ergosterol are administered.

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BRUCELLA INFECTION: CASE REPORT. CULTIVATION OF BRUCELLA FROM THE BILE.

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Various theories have been advanced to explain the chronicity of certain cases of brucellosis. It seems probable that in many, some focus is present from which organisms or their toxic products are periodically discharged. It becomes important, therefore, to discover and remove, if possible, any such focus.

The method described by Amoss and Poston[1] for the isolation of brucella from the stools offers a means of studying the gastrointestinal tract as a possible focus. We are not yet in a position to say whether brucella are eliminated regularly in the stools in practically all acute cases, as is true of typhoid fever; or whether their presence in the stools may be considered indicative of localized gastrointestinal infection with brucella. Intestinal lesions in undulant fever have been described by Bruce[2] and by several other

observers, and we have found brucella in the stools of both chronic and more acute cases.

One would expect to find the gall bladder playing an important part in brucella infections, especially where organisms could be demonstrated in the stools, if an analogy to typhoid fever might be drawn. Eyre[3] describes the isolation of brucella from the gall bladder bile of experimentally infected guinea pigs, and was able to trace the organisms all the way from the duodenum to the rectum, and to isolate them from the feces. By a method of agglutination of mixed growths from the stools with specific serum, similar in principle to that described by Amoss and Poston, he isolated brucella from the feces of a case of undulant fever at autopsy, but was unable to isolate brucella from the feces of 7 living patients.

Tallo,[4] in 1914, considered that the persistent growth of brucella in the gall bladder might be of possible importance in the production of a carrier state following Malta fever, as well as that the infected gall bladder might serve as a focus from which the organisms could be expelled to produce a chronic relapsing type of infection in the individual harboring them. He found that bile is a favorable culture medium for brucella, and was able to isolate brucella from the bile of guinea pigs into which living organisms were intravenously injected. He later[5] found that, though no brucella could be isolated from the blood of his injected guinea pigs after the twelfth day, they could be recovered from the bile as long as thirty-five days after the injection.

Even previous to Tallo's work, Bull and Gram,[6] in 1911, reported a case in which organisms thought to be brucella were isolated from the gall bladder removed at operation. As the reference is somewhat inaccessible, the case reported by them is abstracted in some detail.

The patient was an emaciated woman forty-three years of age. During adolescence she had suffered repeated attacks of rheumatic fever, and was at one time thought to have pulmonary tuberculosis. At the age of twenty, while living in St. Paul, Minn., she had an attack of fever, which though considered typhus at the time, the authors think may have been undulant fever. Two years later, because of vomiting and pain in the abdomen and back, a laparotomy was done and bilateral tuberculous salpingitis found; apparently no pathologic examination was made. When thirty years of age she had hematemesis on one occasion.

At the age of thirty-two years, attacks of pain in the epigastrium and the right upper quadrant of the abdomen began. At first the pain did not radiate, but in later attacks it went through to the back and under the right scapula. She rarely vomited. She was jaundiced during one of the attacks, which came every few months over a period of nine years. The duration of the pain was from one-half to six hours, and it was followed by soreness.

She was admitted to the hospital for operation in 1910. Both liver and spleen were markedly enlarged, as her family physician had reported them to be at least three years previously. The gall bladder was not palpable, but some tenderness was noted over it. Blood examination showed hemoglobin, 55 per cent; red blood cells, 3,190,000; white blood cells, 3000. A few myelocytes were present, but the evidence was considered insufficient

to suggest a primary blood disease. Hepatic cirrhosis was considered unlikely in view of the apparent smoothness of the liver.

At operation a large gall bladder with edematous wall was removed: it contained 30 stones. Culture of the gall bladder contents revealed a small Gram-negative bacillus, identified as brucella. Identification was based on its cultural similarity to a strain of brucella obtained from the laboratory of Kral, and to the agglutination by the patient's serum in dilutions up to 1 to 150 of both this strain and the one isolated from the patient. No anti-melitensis serum was available.

The patient made a good recovery.

We observed a case in which brucella were isolated from the stools, from the bile obtained by duodenal drainage, and from the gall bladder contents removed at operation. Search of the literature has revealed no other cases in which brucella have been isolated from the human gall bladder.

Case Report. H. P., No. 29227, a physician aged fifty-three years, was admitted to the Johns Hopkins Hospital January 27, 1930, complaining of discomfort in the right upper quadrant of the abdomen and intermittent fever, of five months' duration. His family history was noncontributory. Prior to his present illness, he had had measles and varicella in childhood, and repeated attacks of tonsillitis until a tonsillectomy was done at the age of eighteen. At twenty-one years of age he had typhoid fever with no apparent complication. A Neisserian infection at twenty-three resulted in a chronic infection of the prostate and seminal vesicles, for which he was treated every few months. Subsequent to a severe attack of bilateral maxillary sinusitis at thirty-two he had frequent recurrences of sinus trouble. He lived in an institution where raw milk was used from a herd not tested for Brucella agglutinins, but not known to be subject to contagious abortion. He had no contact with swine or goats.

Five months before admission he had an attack of diarrhea, generalized abdominal pain, and fever, which lasted two weeks, and seemed to follow the ingestion of new beets and corn. He had a gastrointestinal Roentgen ray series, with visualization of the gall bladder, both examinations being normal. On a bland diet chiefly composed of milk and eggs, with belladonna and mineral oil, he regained the 10 pounds he had lost, and felt well during a two weeks' fishing trip. However, on returning to work, he noted intermittent discomfort in the right upper quadrant, especially associated with fullness after meals. The pain was never severe and did not radiate. He noted some tenderness on pressing over the area in which the discomfort was localized. Though he had occasional attacks of diarrhea, the stools were never bloody, tarry, or clay-colored. He did not vomit and was not jaundiced. At times he felt chilly but was never sufficiently suspicious of having fever to take his temperature.

Five weeks before coming to Johns Hopkins Hospital he began to feel more chilly, and to have afternoon fever with drenching sweats in the early morning hours. He had no joint pains, but general malaise was marked. After two weeks he was admitted to the University of Maryland Hospital on the service of Dr. Aycock, where he was studied for three weeks. During this time his temperature fluctuated between 98.6° F. at 8 A.M. and 100.4° F. at 8 P.M., except for a period of five days during which the evening temperature was higher, reaching 102° on two occasions. Examination showed only some slight tenderness and spasm in the region of the gall bladder. Leukocyte count was normal, and urine showed only an occasional white blood cell and rare hyaline and granular casts. Phenolsulphonephthalein

excretion was 60 per cent in two hours. Blood nonprotein nitrogen was 41 mg. per 100 cc. Fractional gastric analysis revealed a maximum free hydrochlorid of 46 after seventy-five minutes, and a maximum total acidity of 62 at the same interval after the insertion of the tube. Proctoscopy revealed a slight excess of mucus in the sigmoid, and Roentgen ray studies of the gastrointestinal tract were normal. Blood culture showed no growth after seventy-two hours, but the blood serum agglutinated brucella in dilutions up to 1 to 320. From a specimen of stool sent to Johns Hopkins Hospital by Dr. Maurice Pincoffs for culture, brucella were isolated which were agglutinated by the patient's serum in dilutions up to 1 to 1280, and by caprine, bovine and porcine antibrucella sera in the same dilution. A diagnosis of undulant fever was made and he was transferred to the Johns Hopkins Hospital.

On admission, the temperature was 100.2° F.; pulse 80; respirations, 18; and the blood pressure, 120 systolic and 76 diastolic. Examination revealed a middle-aged man of normal development in a state of good nutrition. Skin showed no eruptions or rose spots, and there was no enlargement of the superficial lymph nodes. Pressure over the sinuses elicited no tenderness, and the sinuses transilluminated well. Upper teeth were absent and the remaining lower teeth had many fillings but appeared to be in good condition. The tonsils were cleanly removed. Lungs were clear and the heart showed no abnormalities. The abdomen was slightly distended. No masses were palpable and there was no muscle spasm. An area of quite localized tenderness to deep palpation was found in the right epigastrium. Liver, spleen and kidneys were not felt. The prostate was not enlarged or tender, but felt somewhat indurated. Seminal vesicles were palpable, and also moderately indurated. Fluid expressed from the prostate showed 20 to 40 leukocytes per high-power field, some in clumps, and the fluid expressed from the seminal vesicles contained a similar number of leukocytes and many actively motile spermatozoa. No organisms were seen in the stained smears, and none were found on culture.

Examination of the blood showed hemoglobin, 90 per cent (Sahli); red blood cells, 4,450,000; white blood cells, 5600; polymorphonuclears, 62 per cent; lymphocytes, 37 per cent; transitionals, 1 per cent. The blood smear was normal. The only noteworthy finding on examination of the urine was an occasional leukocyte. Brucella were isolated from only the first of nine cultures of the urine. The blood Wassermann was negative in ice box and water bath. Repeated study of the stools revealed no gross or occult blood (Benzidine), and no ova or parasites were found. Brucella were isolated from the stools on ten occasions. Two blood cultures taken at the highest points of his temperature in pH 6.6 liver infusion broth and in liver infusion agar of the same acidity showed no growth after sixteen and twenty days, respectively. His blood serum agglutinin titer had risen to 1 to 2560 for bovine and caprine strains, but remained at 1 to 1280 with the porcine brucella antigen.

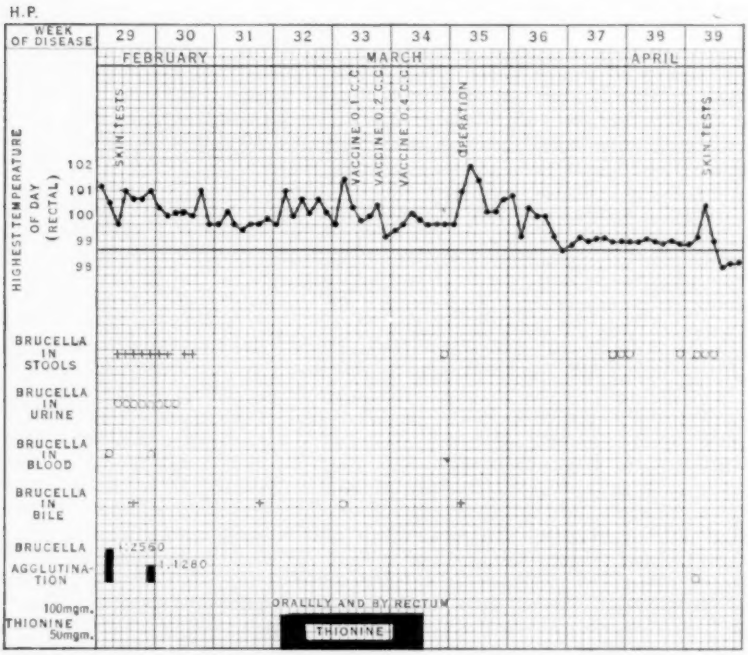
On duodenal drainage, 20 cc. of clear, light-colored bile were obtained, showing no cholesterin crystals, leukocytes or organisms on microscopic examination. Following the introduction of 20 cc. of 50 per cent magnesium sulphate solution into the duodenum, about 45 cc. of dark-brown bile flowed out of the tube. This was also negative on microscopic examination, but on culture in pH 6.6. liver infusion broth brucella were isolated in pure culture. Brucella were again isolated from the bile obtained at one of the two subsequent duodenal drainages. When the "B" bile began to flow following the introduction of magnesium sulphate, he complained of discomfort in the right upper quadrant similar to his previous pain there.

His gall bladder filled after the ingestion of tetraiodophenolphthalein. Barium enema showed a normal colon, and gastrointestinal series was again normal.

He was markedly hypersensitive to the intracutaneous injection of brucella suspensions, showing more marked reaction to the bovine and caprine than to the porcine strain.

Course. He was observed for a period of six weeks prior to operation. During this time his temperature fluctuated as indicated in the accompanying chart, but never rose above 101.5° F.; it was usually essentially normal in the morning and reached the highest point about 8 P.M. Though uncomfortable and weak, he was never prostrated and had no severe pain.

It was shown by Hill and Scott[7] in 1925 that mercurochrome is excreted by the liver and appears in the bile in concentrations bactericidal for Eberthella typhi. They were able to cure rabbits made gall bladder carriers of this organism. Martin and Hill,[8] in 1929, observed improvement in 5 of 8 patients suffering from cholecystitis following intravenous injection of



mercurochrome. On the basis of this work, the intravenous injection of mercurochrome was suggested, but refused by the patient.

His organism was studied for its susceptibility to the bacteriostatic action of thionine and methyl violet as described by Huddleson[9] and found to be more susceptible to thionine. We[10] had previously had some success in eliminating brucella from the stools of patients showing persistently positive cultures by the use of these dyes. Hence thionine was given orally and by rectum in total daily dosage of 110 mg. for a period of seventeen days, and discontinued four days prior to operation, which was decided on at the patient's request. Unfortunately only one stool was cultured for brucella between the time thionine was stopped and the time of the operation. No brucella were found in this specimen. It is difficult to say whether

or not the thionine was responsible for the absence of brucella in the stool at this time.

He also received three small doses of autogenous brucella vaccine.

On March 11, 1930, cholecystectomy and appendectomy were performed by Dr. J. M. T. Finney, Sr., under nitrous oxid and ether anesthesia. The wall of the gall bladder was found to be somewhat thickened, and adhesions bound it firmly to the under surface of the liver; no stones were present. The stomach and duodenum were normal and the spleen not enlarged. Adhesions partially bound down the appendix, which was not indurated or grossly inflamed.

Pathologic examination of the gall bladder revealed some thickening of the wall and moderate infiltration of the muscularis by lymphocytes, but there was little evidence of real inflammation. The appendix showed no active inflammatory process.

Cultures taken just after the organs were removed gave the following results:

Gall bladder bile	Pure culture brucella.
Submucosa of gall bladder	No growth.
Cystic gland	No growth.
Submucosa of appendix	B. coli communis.
Mucosa of appendix	B. coli communis.
Peritoneal surface of appendix	B. coli communis.

His postoperative course was uneventful and convalescence satisfactory. On discharge he was feeling quite fit, had no pain or discomfort, and had practically regained his normal weight.

Seven stools cultured for brucella after the operation were negative. The blood serum contained no agglutinins for brucella at the time of his discharge, April 14, 1930, though he was still hypersensitive to the intracutaneous injection of 0.1 cc. of suspension of brucella.

When last heard from June 10, 1930, he was back at work and felt entirely well.

Discussion. It seems quite likely that the gall bladder plays an important rôle in chronic recurring brucella infections.

It is also probable that carriers exist following undulant fever, harboring brucella in the gall bladder and excreting them in the stools. In view of the rarity of contact infection in brucellosis, it is unlikely that the importance of carriers is as great in the spread of this disease as is the case with typhoid, for example.

In our case the patient was subjectively improved and the stools were apparently freed of brucella by cholecystectomy.

Conclusions. 1. A case is described in which brucella were recovered from the bile removed by duodenal drainage, and from the gall bladder contents at operation.

2. In a patient whose extirpated gall bladder contained brucella, the stools, from which brucella were isolated prior to operation, no longer showed these organisms following cholecystectomy.

NOTE.—We wish to thank Miss Mary A. Poston for her invaluable assistance in the bacteriologic work of this case, and Dr. T. J. Abernethy for his aid in clinical examination.

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THE INCIDENCE OF HUMAN INTESTINAL PROTOZOA.

With Especial Reference to Endamœba Histolytica, in the Residents of the Temperate Zone.

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In association with other investigations (Paulson and Andrews 1930, Andrews and Paulson, 1930) upon human intestinal protozoa the following observations upon incidence were made. It is believed that these findings indicate the probability of a much lower incidence, particularly of Endamœba histolytica in populations resident in large cities in the temperate zone than has been hitherto expressed. The current opinion as to the incidence of intestinal protozoa in residents of the temperate zone, is based primarily upon the results of surveys, most of which were made on individuals living in military, institutional, and semi-institutional situations where the maintenance and spread of protozoal infestations was undoubtedly facil-

itated. According to current textbooks (Craig, 1926; Hegner, 1928) the incidence of Endamœba histolytica in the temperate zone is about 10 per cent.

If this figure represents the actual state of affairs regarding the presence of Endamœba histolytica, one would expect to encounter the parasite frequently in any series of feces examinations conducted upon an unselected sample of the population resident in the temperate zone. Dobell (1917) and Carter, Mackinnon, Matthews, and Smith (1917) have found that a single stool examination per capita reveals about a third of the cases positive for protozoa, consequently the expected frequency of Endamœba histolytica in single stool examinations of a population in which the incidence is 10 per cent should be about 3 cases per 100 individuals. In the series of feces examinations here reported under conditions which will be described, a single case of Endamœba histolytica has been encountered in a group of 522 persons residing in Baltimore, Md., or environs, examined, for the most part, once per capita.

In 1927, the authors reported the comparative incidences of various human intestinal protozoa from defecated stool specimens and from specimens obtained with the sigmoidoscope. In all, 253 individuals were examined, but defecated specimens were available from only 210. These people were an unselected lot of civilians who presented themselves at the clinic for the relief of various and sundry complaints referable to the gastrointestinal tract. Not a single infection with Endamœba histolytica was found in the entire group, though two examinations, that is, one of the sigmoidoscopic and one of the defecated specimen were made on 210 of them. This is significant, since we demonstrated in this study that we were able to improve protozoölogic diagnosis more than threefold by the examination of material from the sigmoid secured through the sigmoidoscope as compared with that of defecated feces.

The present study has been made upon the same sort of material. Individuals coming to the clinic for the first time because they were suffering from some gastrointestinal complaint were given containers with instructions to return a sample of bowel content free from urine upon their next visit, which was ordinarily the next day. The stools were examined microscopically irrespective of the barium content (Andrews and Paulson, 1930) within two or three hours after they had been brought to the clinic. In all, 312 persons living a civilian life and of various ages and nationalities were examined, financially dependent upon a hospital dispensary for their medical assistance. Thus they were people who lived under the least sanitary conditions which obtain in the city, which fact, plus the factor of selection involved in that they were all at the clinic because of gastrointestinal complaints, makes it seem probable that the incidence of intestinal protozoa in such a group would be as high as could be expected in any group of the city population. The inci-

dence of the various protozoa based upon a single stool examination is shown in Table I.

TABLE I.—INCIDENCE OF INTESTINAL PROTOZOA, BASED UPON SINGLE STOOL EXAMINATIONS.

	Number.	Per cent.
Total examined	312	
Negative for protozoa	277	88.8
Positive for protozoa	35	11.2
By Species.		
Endamœba histolytica	1	0.3
Endamœba coli	15	4.8
Endolimax nana	9	2.9
Iodamœba williamsi	5	1.6
Trichomonas hominis	5	1.6
Chilomastix mesnili	3	1.0
Giardia lamblia	11	3.5
Embadomonas intestinalis	1	0.3

Of the positive cases, 24 were single species infestations, 7 were double, and 4 were triple.

A comparison and combination with our previously reported results (1927) is shown in Table II. The figures from the 1927 report are for the defecated specimens of the combined barium and nonbarium groups.

TABLE II.—COMPARISON AND COMBINATION OF 1927 AND PRESENT SERIES OF INCIDENCES OF INTESTINAL PROTOZOA.

	1927 series.	Present series.	Combined series.
Total examined	210	312	522
	Per cent	Per cent.	Per cent.
Negative for protozoa	89.5	88.8	89.3
Positive for protozoa	10.5	11.2	10.9
By Species.			
Endamœba histolytica	0.0	0.3	0.2
Endamœba coli	3.5	4.8	4.2
Endolimax nana	1.9	2.9	2.5
Iodamœba williamsi	1.0	1.6	1.3
Trichomonas hominis	2.9	1.6	2.1
Chilomastix mesnili	1.9	1.0	1.3
Giardia lamblia	1.4	3.5	2.7
Embadomonas intestinalis	0.0	0.3	0.2

Though the total number of cases examined in either or in the combined groups is not great, the correspondence between the results in the two series is quite remarkedly close, and we believe, justifies the conclusion that the incidence of the various protozoan organisms that infest the human intestinal tract in this locality is not as great as is frequently expressed for the temperate zone, even when our figures are tripled to raise them to the basis of 6 examinations per individual. It is possible that the inclusion within each series of individuals who had partaken of barium sulphate for

roentgenological purposes within the week prior to examination has operated to reduce the incidence of these forms (Andrews and Paulson, 1929) but judging from our previous observations (1927) the loss, on the basis of single examinations would not be greater than 5 per cent for the total incidence. The difference between these frequencies of occurrence and those previously recorded probably lies in the fact that the groups heretofore utilized have been for the most part inmates of asylums or orphanages or similar institutions (Boeck and Stiles, 1923) where personal hygiene is defective, on persons of military experience past or present (Kofoid, Kornhauser, and Plate, 1919; Kofoid and Swezy, 1920; Boeck and Stiles, 1923; Riley, 1929) where the possibility of contamination of food by infected flies and food-handlers gives opportunity for widespread distribution of food-borne organisms, or of situations such as mining camps (Faust, 1930) where the population was intensely concentrated and where fecal contamination was common, as judged by the prevalence of ascariasis (Cort, Otto and Spindler, 1930) due to lack of sanitary facilities or training, or in the more remote rural sections where in addition to these situations favorable to parasitic infestation in human beings, primitive conditions sometimes also prevail (Meleney, 1930).

In contrast to the above mentioned groups, the present one is composed entirely of civilians who, while not living under the most hygienic conditions afforded by a large American city, live in family units and not as closely together as do the military and institutional groups. This fact is significant for the possibilities of contact and contamination are greater in the institutional and military groups: one cook may infect scores of individuals. On the basis of the aforegoing, plus improved sanitation and increased facilities for the maintenance of proper personal hygiene in the city, one would expect that the incidence of protozoa would be much less among the civilians, and it must be remembered that this group is more nearly representative of the total population resident in the temperate zone than the military and institutional classes and rural groups. The incidence of intestinal protozoa in such a civilian group as has been described, is probably more nearly representative of the incidence of intestinal protozoa in residents of the temperate zone as a whole than incidences based upon the previously mentioned surveys, inasmuch as most of the population of the temperate zone now is concentrated within large cities.

Summary. A survey for human intestinal protozoa with especial reference to Endamœba histolytica among adults residing in their natural environment in a large American city of the temperate zone (Baltimore), who appeared at our outpatient department for relief from gastrointestinal symptomatology, is reported. This study is distinctive in that the material has come from those residing in their homes, while practically all similar investigations have been among

institutional and military classes, rural groups and from highly concentrated zones of population where fecal contamination was common. While the total numbers of cases examined is not great, the correspondence between the results in two series herein reported is so remarkably close, that we believe that the conclusion is justified that the incidence of the various protozoa infesting the human intestinal tract in this locality is not as great as has been frequently expressed for the temperate zone; and further, that the following incidence among this group of city dwellers is probably more nearly representative of the incidence of intestinal protozoa in residents of the temperate zone as a whole, inasmuch as most of the population of the temperate zone is concentrated now within large cities.

In 522 cases studied, the total incidence of human protozoa infesting the intestinal tract was 10.9 per cent. By species: Endamœba histolytica, 0.2 per cent; Endamœba coli, 4.2 per cent; Endolimax nana, 2.5 per cent; Iodamœba williamsi, 1.3 per cent; Trichomonas hominis, 2.1 per cent; Chilomastix mesnili, 1.3 per cent; Giardia lamblia, 2.7 per cent; Embadomonas intestinalis, 0.2 per cent.

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THE RELATIONSHIP OF FUNGI TO CHRONIC SPLENOMEGALY OF UNKNOWN ORIGIN.

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Interest in the etiology of chronic primary splenomegaly with cirrhosis of the liver and secondary anemia has recently been stimulated by the reports of numerous investigators who believe the disease to be of mycotic origin.

In a previous study of this problem we[1] have reported the isolation of two different kinds of fungi from the spleens of 3 cases of chronic splenomegaly and from 1 case of cirrhosis of the liver. The fungi which were isolated were, however, of a variety different from those recovered from the spleens of similar cases by other investigators. The penicillium recovered from one spleen did not conform to the varieties described in the available literature. This fungus was virulent for hamsters, guinea pigs and rabbits when injected intraperitoneally. Guinea pigs and rabbits died in five or seven days after inoculation. At necropsy nodules were found in the peritoneum, but the spleen and liver showed no histopathologic changes and the fungus could not be recovered by culturing portions of the spleen or liver. Hamsters were more susceptible and died within two or three days after inoculation. A generalized infection with mycotic nodules in the parenchymatous organs occurred. After subcutaneous inoculation animals developed mild localized abscesses and always recovered.

The other variety of fungus which was isolated from the spleen of 2 cases of primary splenomegaly and from 1 case of hepatic cirrhosis also failed to conform to the description of recognized varieties. The mycologic characteristics of this organism suggested its inclusion in the genus helminthosporium. This fungus was without virulence for laboratory animals.

According to several investigators,[2,3,4] the belief that fungi are the etiologic agents of splenomegaly appears to be strengthened by the observation of thread-like structures in certain unusual pigment nodules frequently encountered in enlarged spleens. The pigment deposits were described by Stengel,[5] Gandy[6] and recently by Gamna,[7] and have been designated Gandy-Gamna nodules. The filaments were believed by some to be mycelial hyphæ of the fungus. Branch-

ing filaments and fructification organs were described. Other investigators[8,9] also regarded the filaments as mycelium, but did not attach any etiologic significance to the fungus which they believed to be a secondary invader in a damaged spleen. On the other hand, a number of observers[10,11,12,13] believed the filaments to be merely degenerated tissue fibers occasionally impregnated with iron and calcium salts. Our own studies in collaboration with Hu[14] added more weight to the latter opinion.

We have shown that the appearance of the filaments found in the siderotic nodules of the spleen in a certain case was entirely different from that of the hyphæ of the fungus, which was apparently isolated from that spleen. When sections of spleen were stained by special methods it was evident that many of the iron-bearing filaments found in the nodules were continuous with normal elastic fibers. In other words, the filaments are degenerated tissue fibers impregnated with iron and calcium salts. Furthermore, similar nodules containing filaments were found in the spleens from cases of other diseases as well as in an adenomatous thyroid gland.

Since our previous reports we have had the opportunity to study the spleens from 6 more cases. Three appeared to be cases of cirrhosis of the liver with large spleens and the others chronic primary splenomegaly, 1 of which was probably syphilitic in origin.

Histologic and cultural studies were made of the excised spleens.

A brief description of the cases follows. The patients were all male Chinese.

Case Reports. Case I.—The patient, aged twenty-six years, complained of a growing mass in his left upper abdomen for over two months. He had been losing weight and strength and had occasional epigastric distress with abdominal distention for the past year. He had malaria at the age of twenty years, jaundice at twenty-four years and repeated attacks of bacillary dysentery. There were 3,180,000 red cells and 2000 white blood cells per c.mm. Hemoglobin, 59 per cent (Sahli). No malarial parasites were found. The spleen was easily palpable. Splenectomy was performed, but the patient developed bronchopneumonia, partial intestinal obstruction and died a few weeks later.

The spleen weighed 1065 gm. Grossly the cut surface showed marked congestion and some fibrosis. The trabeculæ were very conspicuous. Histologically it showed a diffuse increase of fibrous tissue. Malpighian corpuscles were smaller than usual and the trabeculæ were greatly thickened. No siderotic nodules were encountered.

Case II.—A man, aged twenty-six years, entered the hospital for a blood examination. He had been in good health excepting that he tired easily, lost a slight amount of weight and was becoming pale. Two weeks before admission to the hospital he noted a sense of distention in the left upper abdomen with some epigastric pain. He had had typhoid fever at the age of eight years and malaria at ten years. Physical examination was essentially negative except for a large firm palpable spleen. A blood count showed 2,720,000 red cells and 1550 white cells per c.mm. of blood with 50 per cent hemoglobin. He suffered two attacks of fever (41° C.) and chilliness, lasting two days each. No malaria or other parasites were

found. A diagnosis of chronic primary splenomegaly was made and splenectomy performed. The patient was discharged a month later much improved, with 4,900,000 erythrocytes and 5000 leukocytes per c.mm.

The spleen weighed 850 gm. Numerous siderotic nodules were found on the cut surface. Microscopically there was moderate fibrosis, thickening of the arterial walls with periarterial hemorrhages, siderotic nodules showing filaments suggestive of mycotic hyphæ and hyperplasia of lymph follicles. A section of liver tissue did not show any cirrhosis.

CASE III.—The patient, aged forty years, complained of abdominal swelling for five months. Several years ago the abdomen was swollen for three or four months and there was slight jaundice present, but he recovered. He was conscious of a mass in his upper left abdomen for the past six or seven years. Seven months before admission to the hospital he vomited about 400 cc. of dark-red fluid, followed by many dark stools. After that his abdomen commenced to enlarge until he was unable to walk. There was no past history of malaria or venereal disease.

The patient was pale, emaciated and slightly jaundiced. The abdomen was greatly distended with fluid. There were frequent bouts of fever, lasting two to eight days and often exceeding 40° C., interspersed with periods of normal temperature. His abdomen was tapped repeatedly. After each tapping the spleen was felt. Erythrocytes, 2,800,000 to 3,200,000. Hemoglobin rose from 27 to 56 per cent after three months' hospitalization with diet and blood transfusion. Leukocytes varied from 1500 to 4000. After splenectomy the erythrocyte count rose to 3,750,000, but the hemoglobin and leukocytes remained unchanged. The ascites recurred and required tapping.

The spleen weighed 720 gm. The cut surface showed prominent Malpighian bodies and trabeculæ. Microscopically there was marked diffuse fibrosis with thickening of the bloodvessels. No siderotic nodules were found. A section of liver tissue removed at operation showed some increase of fibrous tissue, probably early cirrhosis.

CASE IV.—The patient, aged twenty-six years, complained chiefly of distention of his abdomen and diarrhea for fourteen months. After the ascites was tapped three times he was admitted to the hospital for splenectomy. The erythrocytes numbered 5,440,000 and the leukocytes 4800. There were occasional bouts of fever.

There was no improvement after splenectomy.

The spleen weighed 575 gm. The chief change in this spleen was a diffuse fibrosis and hypertrophy of the Malpighian bodies. A section of liver tissue showed extensive fibrosis. Chief diagnosis, Laennec's cirrhosis of the liver.

CASE V.—This patient, aged forty years, complained of swelling of his abdomen for two months, with occasional vague abdominal pain. The abdominal distention was increasing. On examination there was slight jaundice. The spleen was palpable, especially after the withdrawal of 5000 cc. of ascitic fluid. The liver was not palpable. There were 3,740,000 erythrocytes, 6600, 10,200 and 4500 leukocytes per c.mm. of blood. Blood Wassermann, negative.

Soon after tapping the ascites recurred and fever was noted. Splenectomy was performed, at which time the liver was found to be firm and nodular The patient was later discharged unimproved.

The spleen weighed 850 gm. The cut surface showed prominent trabeculæ and many siderotic nodules. Sections of the liver showed a periportal fibrosis. The pathologic diagnosis was nodular cirrhosis of the liver and splenomegaly.

Case VI.—The patient, aged twenty-six years, complained chiefly of abdominal distention, polyuria and polydypsia for six months. There was ascites, glycosuria and hyperglycemia. The spleen was palpable. A penile sore was present and the Wassermann test was positive. Erythrocytes, 3,900,000; hemoglobin, 72 per cent; leukocytes, 1500. After one tapping the ascites never reappeared. The patient's diabetes was treated, and he was given a course of arsphenamin. The red cells increased in number to 4,400,000, but the leukocytes remained at 1700, hemoglobin 70 and the spleen was undiminished in size.

Splenectomy was performed. At operation the liver was found to be small and finely nodular. No biopsy was made.

The spleen weighed 1065 gm. The cut surface showed thickened trabeculæ and fibrosis with many siderotic nodules.

A summary of the cases is given in the table:

Summary of Cases.

		Diagnosis.	Gandy-Gamna nodules.	Fungus recovered.
Cases reported previously[1]	I.	Splenomegaly	Present	Helminthosporium.
	II.	Splenomegaly	Present	Helminthosporium.
	III.	Splenomegaly	Absent	Helminthosporium.
	IV.	Cirrhosis	Present	Penicillium
Cases in present study	I.	Splenomegaly	Absent	Helminthosporium.
	II.	Splenomegaly	Present	None.
	III.	Cirrhosis ?	Absent	None.
	IV.	Cirrhosis	Absent	None.
	V.	Cirrhosis	Present	None.
	VI.	Splenomegaly	Present	None.

Methods. After the spleen was removed it was seared and cut with a hot knife. Small blocks of tissue were cut from various locations of the fresh surface with sterile scissors. The tissue was cut into small fragments and thoroughly ground in a sterile mortar. The pulp was then thinly spread over the surface of Sabouraud agar slants in large 1-inch tubes. From 30 to 40 tubes were inoculated at a time and were incubated at 37° C. for at least one month. Histologic sections were prepared and studied.

Wedges of liver tissue removed at operation were similarly cultured and prepared for histologic study.

At the same time portions of spleen and liver were inoculated into Noguchi's solid and semisolid leptospira media and on ordinary blood-agar plates for the purpose of isolating any other organisms which might have been present. The cultures were incubated in two sets, one at 30° C., the other at 37° C., for a month. Aside from occasional obvious surface contaminants, no organisms were cultivated.

The cut surface of the spleen from 2 of the cases of primary splenomegaly (Cases II and VI) showed numerous siderotic nodules, which are considered by some observers to be pathognomonic of the disease and to be the result of the fungus growth. However, although many of these nodules were present in the portions of

tissue selected for culture, no growth of fungus occurred in any of the 40 tubes inoculated from either case. A helminthosporium-like fungus was cultivated from the spleen in Case I, in which no siderotic nodules were found.

In 1 case of hepatic cirrhosis (Case V) the spleen was enlarged and its cut surface likewise showed many siderotic nodules. They resembled minute pieces of cork embedded in the tissue. Several of these nodules were excised and spread directly on the agar slants. The pulp from other areas also containing many nodules was inoculated in 30 agar tubes. No growth occurred in any.

Cultivation of Splenic Tissue From Other Diseases. Further experiments were made by inoculating tissue from spleens removed at operation and at autopsy on Sabouraud's medium. Eleven spleens were examined from cases of malaria, carcinoma of the liver, miliary tuberculosis, generalized melanosarcoma, cirrhosis of the liver and so forth. No unusual fungi were encountered. A common penicillium occasionally contaminated a tube.

Experimental. Further attempts were made to determine the relationship of the fungi to splenomegaly by inoculating monkeys with cultures of the organisms isolated from the cases reported previously.[1] Nine animals (Macacus sinensis) were used. The fungus was introduced in various ways: (*a*) By direct inoculation into the spleen; (*b*) by injection into the aorta; (*c*) by intraperitoneal inoculation; (*d*) by prolonged feeding.

Protocols.—*Monkey No. 1.* Under ether anesthesia an attempt was made to inject a suspension of the helminthosporium-like fungus into the splenic artery.* This was not possible on account of the small lumen of the vessel. One-half of a Sabouraud slant growth suspended in about 2 cc. of normal saline solution was injected into the abdominal aorta just above the origin of the splenic artery. The aorta below this level was momentarily compressed during the injection.

The monkey suffered no ill effects; no anemia or other changes were noted. After one year the animal appeared to be in good health. Three months later the animal was killed with chloroform. At autopsy a few healed infarcts in the spleen were found.

Monkey No. 2. This animal was injected intraperitoneally with one-half a Sabouraud agar slant of the helminthosporium fungus suspended in 2 cc. normal saline solution. The animal appeared to be ill the day after, but recovered. It lost weight gradually. Two weeks after the first injection the whole growth of an agar slant was injected intraperitoneally. The animal became ill, and the erythrocytes dropped from 5,900,000 to 4,300,000. Temperature, 36.1° C. The leukocytes were unchanged (about 17,000). The animal was emaciated and died after three days.

Except for the finding of a severe intestinal infestation of small round worms, no direct cause of death was determined. The abdominal and thoracic organs were normal. Portions of the spleen were cultivated in

* We wish to acknowledge the assistance of Dr. H. H. Loucks in the surgica operations performed.

Sabouraud agar, but no growth was obtained, even though only a few days had elapsed since the inoculation of a heavy suspension into the peritoneal cavity.

Monkey No. 3. This animal was injected intraperitoneally with 10 cc. doses of a filtrate of the helminthosporium fungus at five-day intervals for two months for the purpose of "sensitizing" the animal if possible. The filtrate was made by growing the fungus in a medium containing 3 per cent maltose, 1 per cent peptone and 0.5 per cent sodium chlorid in distilled water. After one month's incubation the culture was filtered through a Zeitz asbestos filter. The filtrate was used for injection.

No ill effects were noted. The monkey was then inoculated intraperitoneally with one-tenth of an agar-slant culture. After forty-eight days the animal died.

At autopsy the cause of death was not determined. No abnormalities were found in any of the viscera excepting a few peritoneal adhesions, probably resulting from the repeated injections. Histologically there was an acute splenitis and abdominal lymphadenitis. No evidences of the fungus were found. Cultures of the spleen and liver were sterile.

Monkey No. 7. Received 11 intraperitoneal inoculations of one-quarter of an agar-slant growth of the penicillium, over a period of five months. Three months after the first inoculation the spleen was removed and examined. Grossly it was normal, but histologically hyaline necrosis, and hyperplasia of the lymph follicles were found, but no evidence of the presence of the fungus. Portions of the spleen cultivated on Sabouraud agar remained sterile.

The animal was killed after a year. No important changes were found at necropsy.

Monkey No. 8. At operation the spleen was exposed and about one-quarter of the arterial supply was ligated. During the operation the spleen became enlarged and cyanotic, particularly in the lower pole, which was the part most affected by the ligation. About 0.25 cc. of a heavy suspension of a week-old culture of the helminthosporium-like fungus was then injected into the lower pole and also into the upper or undisturbed pole.

The animal recovered and remained well for four months. It then became ill and died one month later.

Necropsy revealed generalized tuberculosis. No other important changes were found excepting many dense adhesions in the abdominal cavity, due to the surgical procedure.

Monkey No. 9. Was fed daily on the growth of a Sabouraud agar slant of the helminthosporium-like fungus for seven months. The animal remained in good health and showed no blood changes ten months after the beginning of the experiment. After sixteen months it was killed with chloroform. At necropsy all organs were normal.

Monkey No. 10. Was inoculated intraperitoneally with a suspension of an old culture containing many spore-like bodies of the helminthosporium-like fungus. Seven doses were given during five months. No untoward effects were noted. However, after six months the animal became very ill and was killed with chloroform.

Necropsy revealed generalized miliary tuberculosis. The fungus was not recovered in cultures of splenic tissue.

Monkey No. 11. Suspensions of fresh cultures of the penicillium fungus in normal saline solution were inoculated intraperitoneally in increasing doses at two-week intervals for twenty weeks. The last dose consisted of the whole growth from an agar slant. The animal remained in good health for seventeen months when it was killed.

At necropsy no important changes were found aside from dense adhesions in the abdominal cavity, the result of the repeated inoculations.

Monkey No. 12. Received intraperitoneal inoculations of the growth of an agar slant culture, at ten-day intervals for one hundred and fifty days. Old cultures containing many spore forms were used. The animal remained in good health throughout the period. The blood count remained unaffected. The monkey was killed seventeen months after the first inoculation. No abnormalities were discovered at autopsy. Liver and spleen cultures were sterile.

Discussion. The possibility that the fungi isolated from the spleens by other investigators were contaminants and had no relationship to the disease was suggested by Langeron.[11] In our own work this question also arose. Several factors, however, indicated that the fungi actually resided in the spleen in cases of splenomegaly regardless of their etiologic significance. These fungi were unusual and were never encountered otherwise during an extensive study of the common air-borne fungi in these laboratories. From the 5 cases yielding the unusual fungi, growth occurred in each instance in only 1 tube out of the 40 tubes inoculated. Cultures from liver tissue from all cases remained sterile, and, lastly, no unusual fungi were isolated from the spleens of 11 cases of other diseases. On the other hand, in spite of rigid technique, the growth of common varieties of fungi or bacteria occasionally occurred in the tubes from time to time, so that it is necessary to admit that an element of uncertainty still remains.

No evidence indicating the relationship of the fungi to the siderotic nodules was found. Fungi were recovered from spleens in which no nodules were found and no fungi grew from spleens containing many nodules. (See table.) Typical pigment nodules have been found in the spleen and in other tissues in other diseases by several investigators and ourselves. Siderotic nodules in the spleens of cats have been produced experimentally by the injection of alcohol.[15] Gamna[7] and McNee[13] have explained the presence of the nodules as the result of small local hemorrhages in the tissue, with subsequent degeneration and deposition of iron and calcium salts. We[14] have shown that the filaments seen in the nodules are not mycelium, but are merely degenerated tissue fibers impregnated with mineral salts. Thus far the recovery of five different varieties of fungi from cases of splenomegaly has been reported by various investigators, which also tends to show that fungi are not the specific cause of the disease. It seems evident then that the siderotic

nodules are not characteristic of chronic splenomegaly and that they are not caused by the growth of a fungus. It is not unlikely, however, that various fungi can and do live in the spleen as saprophytes, especially in a spleen injured by other processes. Numerous investigations by dermatologists have shown that various fungus diseases may be blood borne; therefore, the occasional recovery of fungi from the spleen would not be surprising.

Experimental inoculation of monkeys with cultures of the two species of fungi isolated during our investigation failed to give any evidence of their pathogenicity. Although a few animals died following inoculation, there was no evidence to show that the fungus was responsible. The rest of the monkeys remained well without showing splenomegaly or anemia until they were killed and examined twelve to eighteen months later.

Conclusions. The results of experimental studies indicate that:

1. Siderotic nodules in the spleen are not characteristic of primary splenomegaly since: (*a*) They are found in other tissues and in other diseases as well; (*b*) cases of chronic splenomegaly occur in which no nodules are found in the spleen.

2. Siderotic nodules in the spleen are not caused by the growth or presence of fungi, since: (*a*) Fungi were cultivated from nodule-free spleens and from spleens studded with nodules no fungi were recovered; (*b*) siderotic nodules have been experimentally produced by the injection of alcohol; (*c*) the filaments found in the nodules are not mycelium but are degenerated tissue fibers.

3. Chronic primary splenomegaly is not caused by fungi, since: (*a*) Various varieties of fungi have been recovered by different investigators; (*b*) the disease could not be reproduced experimentally in monkeys; (*c*) aside from the factors mentioned, it has not been satisfactorily proved that the fungi isolated from the spleens are not air-borne contaminants.

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CINCHOPHEN (ATOPHAN) POISONING.

Report of Four Cases.

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The use of cinchophen in the treatment of human disease was first suggested by Nicolaier and Dohrn,[1] in 1908, following the report of experimental data obtained by its oral administration to various members of the mammalian group, including man, from which they concluded that the drug caused an increase in the endogenous formation and the excretion of uric acid. The similarity of the experimental actions of this drug to those of the salicylate group suggested its use in the treatment of disorders of uric acid metabolism.

Brugsch and Horsters,[2] in 1924, demonstrated the cholegogic properties of cinchophen in experiments performed on dogs. Its property of stimulating the flow of bile has been utilized by various subsequent investigators and clinicians in the radiographic visualization of the gall bladder. The spectacular relief of the pain in certain arthritic conditions has led to its widespread use by physicians as a panacea for practically all neuritic and arthritic distress. Unfortunately its use has not always been supervised by the medical profession. The active principle of a number of quack "rheumatism cures" [3,4] has been identified as cinchophen. Its use in the doses advocated is not without danger, as the fatal termination of 3 of the patients whose histories are reported in this paper will attest. The laity have learned to appreciate its analgesic properties and are using large quantities of cinchophen obtained through patent medicines and drug-store purchases. Rezende[5] and Mouzon[6] have both called attention the dangers involved in this widespread, unsupervised self-administration of cinchophen.

Pharmacology. Cinchophen is known chemically as 2-phenyl-quinolin, 4-carboxylic acid. It is widely used under the trade-name of Atophan. In addition, members of the phenyl-quinolin group are being marketed under a variety of proprietary names.

Its mode of action has been the subject of considerable dispute. Klemperer,[7] in 1913, concluded that no satisfactory explanation of

its *modus operandi* had been given, and we have not been able to find in the later literature any satisfactory hypothesis explaining its action.

Nicolaier and Dohrn[1] noted an increase in uric acid excretion ranging from 100 to 332 per cent as compared with an average of 50 per cent following the administration of large doses of the salicylates. They were unable to prove that the increase in endogenous uric acid formation was not associated with an increase in nuclear degeneration, especially of the leukocytes.

Klemperer,[7] in 1913, noted that a number of Atophan derivatives, such as 7-methyl-ester of Atophan, 6-methyl-amido Atophan, a sulphurous acid combination of Atophan and the ethyl-ester of piperonyl Atophan caused alleviation of the clinical symptoms of gout without increasing the excretion of uric acid. He believed that the action was due to a "complex antiphlogistic and analgesic action."

Mendel,[8] using Cohnheim's classical method of studying inflammatory changes in the mesentery of the frog, demonstrated paralysis of the ameboid movements of the leukocytes, followed by complete disintegration of their nuclei after the injection of sodium Atophan into the thoracic lymph sac. From these results he assumed that the increase in uric acid elimination was due to leukocytic destruction *in vivo* with the consequent release of large amounts of nucleoprotein into the blood stream. He referred to the work of Starkenstein and Wiechowski,[9] who studied the irritative action of mustard oil on the conjunctiva of the rabbit, both with and without the previous administration of Atophan, observing that the Atophan-prepared rabbits exhibited no local inflammatory reaction with the topical application of this substance. Starkenstein[10] later attempted to refute the conclusion of Mendel by stating, "The paralyzing action of Atophan on the leukocytes explains, it is true, the depressing effect of this substance on inflammation, but the effect of Atophan on purin metabolism is not an action on metabolism but an influence upon uric acid excretion." He further cited that he and Wiechowski[11] had demonstrated the paralyzing effect *in vivo* in 1920. He concluded from these studies that the action of cinchophen upon inflammation and upon purin metabolism are "entirely independent." A year later Dohrn[12] claimed that a slight leukocytosis followed the ingestion of Atophan during the ensuing four or five hours and subsided within twenty-four hours. From this data, obtained upon himself, he believed that leukocytic destruction played no part in the increase in uric acid elimination.

Weintraub[13] suggested the possibility that cinchophen had a direct action upon the renal threshold for uric acid similar to that exhibited by phlorizin in lowering the glucose threshold.

The action of cinchophen upon the liver has been inadequately studied. Brugsch and Horsters[2] believed its cholagogue effect to be

due to direct hepatic cell stimulation rather than any indirect action through the vegetative nervous system. They experimentally demonstrated an increase in the twenty-four-hour secretion of bile and bile pigments, showing that the action was not merely that of dilution. Mouzon[6] reported an example of partially healed biliary fistula which would intermittently close, causing the appearance of jaundice. Upon the administration of Atophan the fistula would reopen and the icterus disappear. The frequency with which jaundice is associated with other toxic manifestations and the pathologic changes seen in the liver in the 15 fatal cases studied at necropsy, including the 4 cases reported in this paper, show that this cholagogue action is of fundamental importance.

In view of the facts presented, it is somewhat surprising that so few of the standard textbooks on pharmacology and therapeutics mention the possibility of undesirable by-effects from cinchophen administration.

Classification of Toxic Symptoms. It is not our purpose in this article to review all of the reported cases of cinchophen poisoning, but rather to confine our discussion to the fatal cases. The toxic symptoms reported in the 63 cases of poisoning which we have been able to collect from the literature may be roughly classified into four groups: (1) Cutaneous manifestations, such as pruritus, angioneurotic edema, urticaria, macular and papular rashes, first reported by Phillips[14] in 1913; (2) anaphylactoid reactions characterized by neurocirculatory disturbances associated with rapid pulse and lowered blood pressure following the ingestion of single doses of cinchophen, as mentioned by Scully[15] in 1924; (3) gastrointestinal disturbances including simple aphthous ulcers in the mouth, pyrosis, nausea, vomiting and diarrhea, reported by Schroeder[16] in 1922, and (4) liver involvement as indicated by the appearance of jaundice, first noted by Worster-Drought[17] in 1923. Different degrees of hepatic damage, ranging from transitory icterus to acute hepatic degeneration (acute yellow atrophy) have been reported. In this connection it is interesting to note that all of the fatal cases studied at necropsy have shown striking pathologic changes in the liver.

Review of the Fatal Cases. The accompanying table presents a brief analysis of the 15 fatal cases reported in the literature, including the 4 here presented. It may be seen that a fatal termination has followed the taking of as little as 37.5 gr. (Biloptin, gm. v, equal parts of sodium salicylate and cinchophen). Eight cases presented icterus as an early evidence of toxicity. Clay-colored stools have not been associated with the jaundice in any of the fatal cases. Gastrointestinal disturbances varying from pyrosis to nausea and vomiting were seen in 12 of the 15 fatalities. The liver in every case that has been studied at necropsy has shown degenerative changes characteristic of one or more of the phases of acute yellow atrophy.

Number.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Necropsy findings.
1 . .	Willcox, 1926 (Ref. 18)	Atophan gr. v t.i.d. for 7 days	105 gr.	Onset with icterus in a few days which progressed to icterus gravis; died in 28 days	Not given.
2 . .	Wells, 1926 (Ref. 19)	Atophan, gr. v t.i.d. for 135 days	2025 gr.	Onset with vomiting in three months; pain over gall-bladder area, followed by jaundice; coma appeared the following day and death occurred two days later	Liver shrunken and small and showed yellow atrophy with absence of liver tissue.
3 . .	Hitzenberger, 1927 (Ref. 20)	Biloptin (Atophan qi-iodid), gm. v	37.5 gr. (Atophan)	Onset with malaise, vomiting and fever which was followed by progressive jaundice; became comatose on eighth day and expired following convulsion on the tenth day	Liver swollen, smooth and softened; marked round-cell infiltration with necrosis of adjacent hepatic cells.
4 . .	Singer, 1927 (Ref. 21)	Biloptin, gm. v	37.5 gr. (Atophan)	Onset in twenty-four hours with persistent vomiting followed by progressive jaundice; expired in fourteen days	Liver not described grossly; microscopic showed marked round-cell infiltration; there was associated hemorrhagic nephritis and recurrent endocarditis.
5 . .	Rake, 1927 (Ref. 22)	Atophan	Excessive amount	Onset with sharp epigastric pain, vomiting and jaundice; liver tender and bile present in feces; became comatose and died in forty days following initial symptoms	Liver weighed 1150 gm.; capsule was wrinkled; there were many large irregular areas of regenerating liver tissue; microscopic examination showed increased periportal fibrosis with round-cell infiltration; much fatty degeneration of hepatic cells.
6 . .	Lowenthal, *et al.*, 1928 (Ref. 23—Case I)	Atophan, gr. vii t.i.d. for 6 months	2700 gr.	Onset with mild jaundice in five and a half months; stools retained their color; delirium, coma and death followed in one week	The liver weighed 538 gm. and was of ochre-yellow color with multiple small red areas; microscopic examination showed moderate lobular cirrhosis with necrosis and fatty metamorphosis of liver cells.
7 . .	(Case II)	Atophan, gr. vii ss t.i.d. 3 days a week for 2 months	575 gr.	Onset of jaundice two weeks after stopping drug; jaundice deepened with death in eighteen days	Liver weighed 744 gm.; typical ochre-yellow color studded with minute red areas; microscope showed areas of hepatic cell necrosis with round-cell infiltration.
8 . .	Sutton, 1928 (Ref. 24)	Cinchophen	75 tablets	Onset with nausea, vomiting and mild jaundice; tenderness in right upper quadrant; liver dullness diminished; edema of face and ankle; expired in six weeks after onset	Liver showed circumscribed yellow areas against depressed red areas; yellow areas about 50 per cent of surface; microscope showed yellow area composed of liver cells filled with fat; red areas showed increased connective tissue with hemorrhage and mononuclear infiltration.
9 . .	McKinney and Weir, 1928 (Ref. 25)	Atophan	Unknown	Onset with gastrointestinal upset fol-	Liver weighed 1035 gm.; gross and

9	McVicar and Weir, 1929 (Ref. 25)	Atophan	Unknown	Onset with gastrointestinal upset followed in two weeks by progressive jaundice; expired one month after onset	Liver weighed 1035 gm.; gross and microscopic showed acute yellow atrophy.
10	Reichle, 1929 (Ref. 26—Case I)	Cinchophen	Probably about 1500 gr.	Onset of first attack with vomiting, fever and diarrhea; eight months later after further dosage; another attack with gingival hemorrhage, fever, gastrointestinal upset, rash and apathy; death in one month	Liver weighed 1950 gm.; large number of irregular, firm yellow areas; microscopic showed fatty metamorphosis with increase in connective tissue; round-cell infiltration and hemorrhage associated with fatty change in kidney.
11	(Case II)	Cinchophen, xv gr. t.i.d. or q.i.d.	7050 gr.	Onset with epigastric pain and tenderness; three weeks later had nausea, vomiting and icterus; convulsions on the sixth week followed by death	Liver weighed 575 gm. and was studded with minute yellow nodules surrounded by red firmer areas; microscopic showed hepatic cell regeneration with deposit of fat; connective tissue proliferation with round-cell infiltration.
12	Parson and Harding, 1930 (Case I)	Cinchophen	700 gr.*	Onset with progressive weakness, nausea, vomiting and jaundice; bloody diarrhea one week before death; coma followed by death four weeks after first symptoms	Liver weighed 450 gm.; irregular areas of yellow color against firm, red, granular background; microscopic showed hepatic cell regeneration with fatty change and connective-tissue proliferation with round-cell infiltration.
13	(Case II)	Cinchophen	Unknown	Onset with weakness, nausea and progressive jaundice; pronounced vomiting, coma and death on seventh day of illness	Liver weighed 720 gm.; nodular surface and bile-stained; microscopic showed extensive necrosis of liver cells with proliferation of bile ducts and connective-tissue and round-cell infiltration.
14	(Case III)	Cinchophen, gr. 7.5 t.i.d.	1950 gr.	Onset with epigastric pain, nausea, vomiting, pain in right side, skin eruption, dyspnea and jaundice; became progressively worse with the appearance of local convulsions; died in eight days	Liver weighed 735 gm.; nodular yellow areas surrounded by normal-appearing liver tissue; microscopic showed extensive necrosis and hemorrhage.
15	Parsons and Harding, 1930 (Case IV)	Cinchophen	Unknown	Onset with malaise and mild jaundice; icterus became marked and was associated with nausea and vomiting; mental confusion developed and death occurred nine days after the onset of symptoms	Liver weighed 700 gm.; it was soft, flabby, and had a mottled-yellow and red color; microscopic examination confirmed the diagnosis of acute yellow atrophy.

* Estimated from directions sent with the mail-order "treatment."

Case Reports. CASE I.—*History.* Mrs. H. B., aged sixty-five years, entered the Los Angeles General Hospital on October 13, 1929, complaining of progressive weakness, vomiting and jaundice. She had suffered from chronic arthritis for twenty years and had tried many patent medicines. Four months previously she began taking a mail-order cure* for arthritis, which gave marked relief from the pain without any noticeable untoward symptoms. Three weeks before entrance the progressive weakness and malaise appeared. Eight days before admission she began to vomit everything she ate and simultaneously the joint pains disappeared. The exact time of onset of the icterus was not noted by the patient. The past history included the presence of eczema since the age of sixteen years and complete alopecia for twenty-two years. She had never been pregnant.

Physical Examination. Revealed a white female presenting the typical picture of advanced arthritis deformans, moderate icterus and apathy. The heart and lungs were normal. The pulse was 100. The blood pressure was 128 systolic and 80 diastolic. The area of liver dullness was not increased. The patellar and biceps reflexes were absent. The urine contained a few red blood cells and pus cells. The spinal fluid was normal. The Wassermann reaction on both the blood and the spinal fluid was negative.

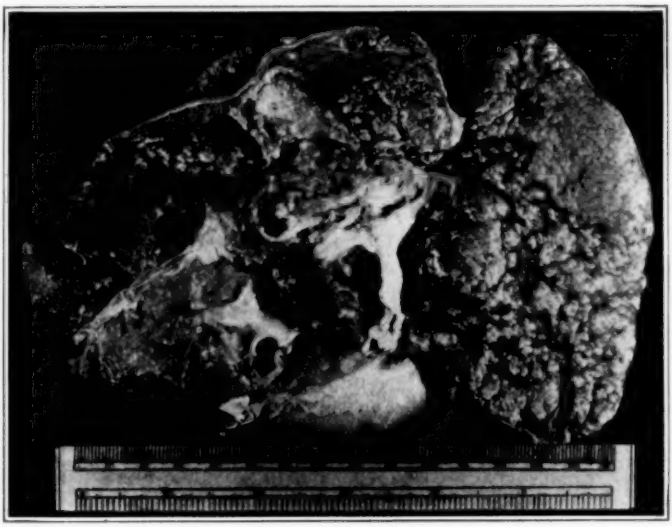
Progress. Her condition remained unchanged during the ensuing five days except that the stools became semiliquid, bloody and of increased frequency. On the sixth day after admission to the hospital she passed into coma following the vomiting of much undigested, blood-tinged food. The temperature was normal; the pulse, 120. A small amount of albumin was present in the urine. The blood count was normal and showed a nonprotein nitrogen of 50 mg. per cent and a carbon dioxid combining power of 27.7 vol. per cent. Her condition remained unchanged for four hours and was followed by death without the return of consciousness.

Necropsy Findings. L. A. G. H. 6067. Examination performed one and three-quarter hours after death. The body appeared poorly nourished. There was complete absence of hair over the entire body. Many white atrophic scars were present over the lower extremities. There was slight edema of the feet and ankles. A definite icteric tint was noted over the entire body, which was most marked in the scleræ. The joints of both the upper and lower extremities showed hypertrophic arthritic changes with a moderate amount of muscular atrophy. A moderate degree of purulent bronchitis was present. The kidneys were comparatively normal except for a minor degree of cloudy swelling. The gastrointestinal tract showed a small diverticulum of the duodenum and numerous small hemorrhagic areas over the tips of the rugæ of the small bowel. The contents of the colon were definitely yellow. The liver weighed 450 gm. It was of flabby consistency. The capsular surface presented many slightly raised areas, which varied in size from 5 mm. to several centimeters in diameter. These nodules were definitely yellow as contrasted with the remaining firm tissue, which was reddish-brown. About three-fourths of the surface made by cutting was composed of these yellow, hyperplastic areas (see photograph).

Hematoxylin and eosin stains of blocks removed from the nodular, hyperplastic-appearing areas showed the major portion of each lobule as an area of marked vacuolization of the liver cells, appearing like fatty infiltration. At the periphery of the lobule was a more or less narrow zone of liver cells, containing varying numbers of droplets; the cells under low-power appearing fairly normal. There was moderate bile-duct proliferation in this zone. Much of the connective tissue was young, showing fibroblasts. The cellular infiltration consisted chiefly of small mononuclear leukocytes, with a few

* Van Ard Sanatorium, Chicago.

polymorphonuclears and eosinophils. Occasional focal necroses were seen at the periphery of the lobules. The first impression received from a low-power examination of the sections from these hyperplastic areas was that of an extensive fatty infiltration. Scarlet-red stained the droplets a bright red, while Nile-blue stained them a deep blue, almost black; so that one concluded that the material was either soap or fatty acids. In hematoxylin and eosin stains of blocks removed from the red, depressed, fibrous areas, the periphery of the lobule was outlined by numerous proliferating bile ducts, associated with a rather marked cellular infiltration, consisting of small lymphocytes and a few eosinophils. The remainder of the lobule showed no normal liver cells but was made up of a loose framework of endothelial cells, probably from the sinusoids, among which were large numbers of red blood corpuscles and occasional Kupffer cells.



Liver, under surface, Case I.

Comment. The above patient showed the edema of the ankles as mentioned by Sutton.[24] The gross appearance of the liver is explained by the microscopic findings. The areas of almost complete destruction of the liver are firm, fibrous and red, the color being due to the great number of red blood cells. The surviving liver cells are so laden with fat as to appear yellow and compose the nodules seen in the gross.

CASE II.*—*History.* Mrs. A. W., aged sixty-seven years, sister of Case I entered the Seaside Hospital, Long Beach, Calif., on November 13, 1929. She had not been well for several months and upon the advice of her sister, Mrs. H. B., had been taking medicine from the same mail-order house.† The patient had noticed slight icterus upon three occasions during this

* We are indebted to Dr. Benjamin M. Mikels for permission to publish this case.
† Van Ard Sanatorium, Chicago.

period of treatment which had cleared each time without change in drug therapy. Five days before entrance she complained of severe weakness, nausea, headache and painless jaundice. The icterus gradually deepened until entrance to the hospital. On the day of admission she became drowsy, had pronounced nausea and vomiting, and lapsed into coma during the afternoon.

Physical Examination. There was profound icterus, Cheyne-Stokes respiration and urinary retention. The pulse was 124 and the blood pressure was 112 systolic and 74 diastolic. The temperature was normal. The liver dullness was definitely diminished. The deep reflexes were absent. The urinary findings were normal. There was a leukocytosis of 13,000 with 80 per cent polymorphonuclears, but the blood count was otherwise normal. The Wassermann reaction was negative. The icterus index was 45 with positive direct and indirect van den Bergh reaction. The spinal fluid was normal.

Progress. The patient's condition remained unchanged during the ensuing twenty-four hours. The blood pressure then rapidly declined, the pulse became irregular and the coma deepened. Death followed without the regaining of consciousness.

Necropsy Findings. (Examination performed by Dr. Benjamin M. Mikels.) The body was that of an obese white female with marked jaundice. There was passive congestion of the lungs. The heart and aorta showed marked arteriosclerotic changes. The abdominal viscera were all normal with the exception of the liver. This organ weighed 720 gm. The capsule was rather loose and wrinkled. The external surface as a whole showed rounding of the margins and had a slightly nodular appearance, due to great numbers of 2- to 5-mm.-sized light-green areas seen against gray depressed areas of similar size. The surface made by cutting had a finely mottled gray-green color. This appeared to be due to an increase in the perilobular connective tissue and marked decrease and distortion of the lobules, which appeared light green. In areas the fibrous tissue increase was sufficiently marked that the lobules were very minute. No large foci of parenchymatous hyperplasia with depressed fibrotic areas between, were seen as in the liver of Case I.

Sections stained with hematoxylin and eosin, when viewed under low-power, gave a first impression of atrophic cirrhosis of the liver that had stained very poorly or had undergone marked postmortem changes. The lobules were irregularly divided into varying-sized areas by bands of faintly stained connective tissue. Closer observation showed these to consist of fibroblasts and their fibers, proliferating bile ducts and marked cellular infiltration consisting chiefly of small lymphocytes. The liver cells composing the islands of tissue between the fibrous bands showed extensive necrosis, while the less degenerated cells were deeply pigmented with bile. Many bile thrombi were seen in the capillaries among these cells. Pathologic fat deposits were not prominent in the hepatic cells but macrophages containing fine fat droplets were frequent in the proliferating fibrous tissue, and stained deep red with scarlet red, while the Nile-blue stained them deep blue, almost black. The lipoids in the liver were thus soaps or fatty acids.

Comment. The finely nodular appearance of the liver was due to the connective-tissue proliferation, while the icterus accounted for the green pigmentation. This liver showed what might be called "toxic cirrhosis," a term Reichle[26] used to describe the liver of his cases.

CASE III.*—*History.* Mrs. M. W., aged forty years, entered the Santa Barbara Cottage Hospital on August 29, 1929, complaining of jaundice, cough and dyspnea, loss of appetite, full ache in right side, a skin eruption and light-colored stools. She had taken thirteen boxes of Atophan for rheumatism during the previous six months. She had had two vomiting spells recently, associated with marked epigastric distress.

Physical examination revealed a well-nourished white female with marked jaundice and moderate anasarca. There was a maculopapular eruption over the face and chest. The lungs showed passive congestion. There was a harsh apical systolic murmur which was transmitted to the axilla. Epigastrium and upper right abdominal quadrant were tender. The blood count was normal and showed a nonprotein nitrogen of 57.1 mg. per cent. Icterus index was 60. The blood Wassermann reaction was 3+. There was a moderate albuminuria and urobilinuria. Stools were of normal color.

Progress. On September 1, 1929, the nausea and vomiting increased and the patient appeared drowsy. These symptoms increased during the next twenty-four hours and in addition, choreiform twitching of the muscles of the neck and upper extremities appeared. The reflexes were not altered. A diagnosis was made of liver damage due to Atophan. The patient's condition became progressively worse and death occurred on September 6, 1929.

Necropsy Findings. (Examination performed by Drs. Richard E. Evans and Harold P. Schwalenberg.) The skin and conjunctivæ were markedly jaundiced. Right pleural space contained 1580 cc. of clear, yellow fluid, the underlying lung being collapsed. Both lungs showed a moderate degree of pulmonary edema. There were 584 cc. of clear fluid in the peritoneal cavity. The essential intraäbdominal pathology was found in the liver. Liver weighed 735 gm. and had a wrinkled capsule; the under surface was mottled with regions of yellow up to about 10 per cent of its area. Broad surfaces, made by cutting the liver, are made up almost 90 per cent by yellow lobulated regions, having the appearance of pancreatic tissue. Between these was grossly normal parenchyma, the lobules of which were clearly defined.

Microscopically the liver showed extensive necrosis so that over 70 per cent of the liver parenchyma was destroyed and replaced by regions of necrotic detritus and red blood cells. In these regions remnants of bile ducts could be identified. The remaining cords of liver cells appeared atrophic.

Comment. The pathologic changes in the liver were similar to those found in Case I. Agonal convulsions have previously been reported by Hitzenberger[20] and Reichle.[26]

CASE IV.†—*History.* Mrs. E. H., aged forty-six years, white, entered the Seaside Hospital, Long Beach, Calif., on July 1, 1928. For the past six years she had suffered from arthritis of the knee joints, which became progressively worse, necessitating her walking with a cane. Four years prior to entrance to the hospital a diagnosis of Amœba histolytica infestation had been made, but she had received little treatment. Following this she developed symptoms suggesting disease of the gall bladder. Two years before admission the gall bladder and appendix were removed but with no improvement in her arthritic symptoms.

* We are indebted to Dr. Richard E. Evans for permission to publish this case.

† We are indebted to Dr. Fred B. Clarke, of Long Beach, for permission to publish this case.

For an undetermined period she had been taking a mail-order cure for rheumatism.* Five days before entering the hospital she had complained of not feeling very well. She had noticed that she had not passed much urine and that she was slightly jaundiced. This was not accompanied by chills or fever. Two days later she developed some nausea and vomiting and the jaundice became more and more marked until at the time of admission it was extreme. At this time she was also mentally confused.

Physical Examination. The patient was obviously desperately ill and markedly jaundiced. There were no excoriations from scratching. She was a large, well-proportioned woman, weighing approximately 180 pounds, but did not appear overweight. There was a decided hypertrophic arthritis of the knee joints. Moderate edema of the legs had been present for some time. The breath was foul. The heart was slightly enlarged. The pulse was 70; the blood pressure was 140 systolic and 80 diastolic. The upper limit of the liver dullness was very indefinite and was about 2½ inches lower than normal. Her confused mental state made her care difficult.

Examination of the blood showed a normal red cell count, leukocytosis ranging from 16,000 to 17,000, with 83 per cent polymorphonuclear neutrophils. The icterus index was 75. The van den Bergh gave a negative direct and a strongly positive indirect reaction. The bleeding time was slightly prolonged; the coagulation time was eight minutes. Fragility test was normal. Blood Wassermann was negative. The nonprotein nitrogen was 73 mg. per cent. Leucin and tyrosin crystals were found in the urine. The pulse rate varied from 90 to 120 and her temperature ranged from 97° to 99° F. She died on the fourth day. The clinical diagnosis was acute yellow atrophy of the liver.

Necropsy Findings. (The examination was made by Dr. Benjamin M. Mikels.) It was restricted to the abdominal cavity. The body was that of a large, not obese, white female weighing about 180 pounds and showing marked jaundice. The liver weighed 700 gm. and appeared extremely small in proportion to the large size of the body; the capsule was not thickened and the surface had a mottled yellow and red color; the organ was very friable and soft. The gall bladder was absent. No biliary obstruction was found. The other abdominal viscera showed little gross pathology.

The gross diagnosis of acute yellow atrophy was confirmed by microscopic examination.

Comment. This is a clear case of acute yellow atrophy of the liver, the diagnosis being confirmed by postmortem examination. This is the third case in which one quack concern, exploiting a mail-order "cure" for rheumatism, is responsible.

Summary. 1. Fifteen cases of fatal cinchophen poisoning have been recorded, including the 4 here reported.

2. Striking pathologic changes in the liver have been found in all of the fatal cases studied at necropsy.

3. The total amount of the drug taken in these cases has varied from 37.5 gr. to 7050 gr.

4. Intensive dosage with cinchophen may produce acute hepatic degeneration. Long-continued administration of the drug in moderate doses may result in subacute and chronic hepatic degeneration.

* The A. H. Cass Company, Chicago.

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REVIEWS.

LABORATORY MEDICINE. By DANIEL NICHOLSON, M.D. Pp. 433; 108 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $6.00.

ACCORDING to the author "the aim of this book is to provide, in detail, information on the indications, method, and interpretation of useful tests that a practitioner should be able to perform," and to outline "the principle and interpretation of the more highly technical diagnostic procedures." The tests described are reliable and cover most of the field satisfactorily. The last chapter includes a list of the equipment necessary for setting up an office laboratory. The description of each procedure is followed by a discussion of its interpretation. The indications for laboratory tests are given tabular form. Tables of normal values are found inside the front cover. A limited number of references to special articles are included. The book should be quite useful to the practitioner who wishes to conduct his own laboratory. G. R.

THE PATHOLOGY OF DIABETES MELLITUS. By SHIELDS WARREN, M.D., with a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 212; 85 illustrations. Philadelphia: Lea & Febiger, 1930. Price, $3.75.

THIS book fills a real need in making readily accessible the data on the morphologic pathology of diabetes, discussed in the light of our clearer understanding of the disease derived from the use of insulin.

The author discusses systematically the various changes associated with diabetes, making references to the most important literature, and analyzing from many angles the data he has accumulated from 300 autopsies on diabetics, most of which are autopsies on Joslin's patients, supplemented by his study of records and tissues of autopsies done elsewhere.

Points of particular interest are the pathologic conditions which are the immediate causes of death in diabetes since insulin has been used; the histologic distribution of glycogen; the distribution and character of the arteriosclerotic changes in diabetes; the morphologic evidences of abnormal fat metabolism; and the comparison of the

pancreas in juvenile diabetics with that of elderly diabetics, and the changes in the islands which may occur in persons without diabetes.

Numerous excellent photomicrographs and photographs of gross material add greatly to the interest of the book.

It is evident that very little real advance has been made in the morphologic study of diabetes since the time of Opie's observations, except that the longer duration of life in diabetics treated with insulin has rendered more distinct the secondary changes complicating this disease.

The author theorizes to a certain extent, giving his own and others' interpretations of some of the unsolved riddles of diabetes; but the book deals essentially with concrete morphologic findings, and, as such, is a very readable, scholarly survey of the present state of our knowledge of this disease. I. Z.

SURGICAL DIAGNOSIS, VOL. III, ALSO INDEX. By 42 American Authors. Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 1044; 446 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $35.00, set of 3 volumes.

VOLUME III begins with a section on Diseases of the Thorax by Graham, which is really a summary of the excellent work done by the author on this subject. The physics and physiology of respiration are fully explained before entering into a discussion of the diseases which affect them. The chapter is followed by a short one on the technique of Bronchography by Ballon.

Olch has written the chapter on the Diseases of the Breast in masterful style. His discussion of cystic mastitis is excellent. He believes "the chief complication of this disease is its transformation into carcinoma." He recommends removal of the involved breast in the menopausal age where definite chronic cystic mastitis has showed no signs of regression over a reasonable period of observation. Frozen section diagnosis, holds, offers no information that cannot be obtained by gro examination, and in doubtful cases he recommends a mammectomy, fixation of several sections of breast tissue and examination of well-cut and stained slides "at one's leisure and under no pressure."

Graham's chapter on the Liver and Bile Passages gives the best of the material presented in his recent book on the subject. The physiology of these organs is well described and the etiology and diagnosis of their various diseases. He gives an excellent analysis of his own and other's experience with Roentgenological visualization of the gall bladder. The last part of the chapter is given over to a description and evaluation of the various tests of liver function.

The diseases of the Pancreas are dealt with by Muller followed by a short chapter on Pancreatic Function Tests by Elman. Shipley has written a good section on Diseases of the Rectum and Anus.

One of the most novel chapters in the whole work is that by Hinman on Diseases of the Genito-urinary Organs. His view is that a monograph only is large enough to discuss the diagnosis of genito-urinary diseases, and that these disorders should really be diagnosed and treated by specialists in that field. Hence he presents outlines by the use of which one may make presumptive diagnoses, and he mentions diagnostic procedures which will give positive findings. With this more or less general discussion, the reader is furnished with a list of the possible diseases affecting the various parts of the genito-urinary tract. No description of these disorders is afforded but a short bibliography is supplied for each anatomical part. The value of such a chapter is to be doubted where a library is not available.

Rose gives a short chapter on his work on Bladder Pressure.

The diagnosis of Diseases of the Nervous System is dealt with by authorities in their fields; Dandy on the Diseases of the Skull, Brain, and Meninges, Adson on the Spinal Cord, Lewis on the Peripheral Nerves and Ransom on the uses of surgery in the Sympathetic Nervous System.

The whole work is well edited and illustrated. Written as it is by 42 of America's leading surgeons, it affords an interesting study in author's style, as well as a dependable reference of surgical diagnosis and experience. It should prove of value not only to the surgeon, but also to all who must diagnose surgical diseases, and is without doubt the most comprehensive modern work in its field.

L. F.

Clio Medica. Vol. IV. Internal Medicine. By Sir Humphry Rolleston, Bart. G.C.V.O., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D. Pp. 92. New York: Paul B. Hoeber, Inc., 1930. Price, $1.50.

The Editor of "Clio Medica," a series of invaluable and fascinating Primers relating to the History of Medicine, has been fortunate in his selection of author for the volume on "Internal Medicine." Sir Humphry Rolleston is a world renowned physician and author and his deserved popularity is as great in North America as in the British Isles. Doctor Rolleston has accomplished a difficult task. He has given a brief but comprehensive survey of the history of physic and has embellished the thesis with the charm that characterizes all his writings. Our beloved Osler believed that medicine is best taught from the evolutional standpoint and was fond of quoting Fuller's statement "that history maketh a young man to

be old without either wrinkles or grey hairs." This inexpensive little book, like the other volumes of "Clio Medica," will prove "an easy path to medical knowledge through medical history."

E. B.

THE UNIVERSITY OF CHICAGO ORIENTAL INSTITUTE PUBLICATIONS. THE EDWIN SMITH SURGICAL PAPYRUS, BEING VOLS. III AND IV OF VOL. I. HIEROGLYPHIC TRANSLITERATION TRANSLATION AND COMMENTARY. Pp. 596; 8 plates; VOL. II. FACSIMILE PLATES AND LINE FOR LINE HIEROGLYPHIC TRANSLITERATION. Pp. 13; 22 plates. Edited by JAMES HENRY BREASTED. Chicago: The University of Chicago Press, 1930. Price, $20.00.

THE discovery at Luxor in 1862 by Edwin Smith of this papyrus—the oldest known medical document—was an event of major importance to the history of science. It was not until 1920, however, that its importance was recognized, when the New York Historical Society, to whom it had been presented after Smith's death, invited Breasted to translate it. Its careful and protracted study over a number of years by the foremost of living Egyptologists and now its presentation in such complete and even sumptuous form by the University of Chicago Press not only perpetuate the value of Smith's discovery, but make available invaluable material for the archæologist and some fascinating reading for the ordinary reader.

"In this document we have disclosed to us for the first time the human mind peering into the mysteries of the human body," and yet even this early the recognition of intelligible physical phenomena is found replacing witchcraft as the cause of disease. While the papyrus, which is here so splendidly reproduced and explained, dates from the seventeenth century B.C., and is anonymous (having lost both beginning and end), Breasted believes that it is based on a manuscript written at least a thousand years earlier, possibly by Imhotep, the earliest known physician. In the more than 400 lines that survive, the copyist presents in hieratic script a series of 48 carefully discussed surgical cases, beginning at the top of the head and proceeding downward through the thorax to one case of damage to the spine. What a loss that the copyist did not at least include the section on the abdominal organs! We learn that history taking and physical examination were routinely performed as the basis for diagnosis, and that all cases were divided into 3 categories—ailments successfully treatable, possibly curable and untreatable. The treatment recommended was purely mechanical in 3 cases, a combination of surgery and medical applications in 20, and applications only in 19. In 16 cases, no treatment at all is suggested, a unique occurrence in Egyptian papyri. While it is obviously impossible to refer to details in the limited space available, I cannot

refrain from mentioning the reference to the pulse in the Gloss of Case 1, which apparently indicates not only considerable knowledge of the action of the heart and bloodflow 5000 years ago, but also that the actual pulse rate perhaps was being counted some 2500 years before Democritus and Herophilus. Reference in the Ebers Papyrus to a similar discussion, gives a clue to the possible title of the Smith papyrus as the "Secret Book of the Physician."

While the text of the Foreword, Special Exploratory Notes and the two Introductions will doubtless prove most attractive to the non-Egyptologist, he will also find much of interest in the translation and commentaries of the individual cases and in the 32 facsimile plates and hieroglyphic transliterations of the second volume.

We may indeed feel proud of this new evidence of American scholarship and scientific enterprise. E. K.

History of Haitian Medicine. By Robert P. Parsons, Foreword by Edward R. Stitt. Pp. 196; 21 illustrations and map of Haiti. New York: Paul B. Hoeber, Inc., 1930. Price, $2.25.

Elaborated from an article appearing in the May 1929 issue of the *Annals of Medical History*, this book puts more adequately on record the medical vicissitudes of a romantic island and adds the not unimportant events of the past two years. Considering the 3 periods into which the history naturally falls: the French colonial period (two centuries ending in 1804) is covered in 2 chapters totaling 36 pages, the period of independence in 1 chapter of equal length, while the rest of the book is devoted to the fifteen years of the American occupation. And this is probably a fair division; for in spite of the glamor surrounding the tom-toms of Papa Legba, the voodoo rites, and the soulless Zambies—a colorful note with which the author is obviously in considerable sympathy—nevertheless the unequalled advances in public health that have taken place since the American occupation in 1915 constitute matters of far greater importance in medical history. As Admiral Stitt says in his Foreword "in the short space of ten years an unspeakable hotbed of diseases, from the ravages of which some 3 million people in Hayti were weakened and crippled, has in a large measure been eradicated." The effect of soap, salvarsan, sunshine and sanitation in reducing the almost universal infestation by yaws, intestinal parasites and other endemic diseases, is in itself a lesson in public health that could well be studied by more highly civilized nations. The part that our Navy Medical Department has played in this sanitary revolution is one of which we may all be proud; this account by one who played no small rôle in the action, is correspondingly welcome. E. K.

La Rate, Organe Réservoir. By Leon Binet. Pp. 116; 17 illustrations. Paris: Masson et Cie, 1930. Price, 20 Fr.

Finding in 1926 that the transient polycythemia of asphyxia was absent in splenectomized animals (Barcroft's reservoir function), the author planned a number of explanatory studies, which are here reported as follows: (1) the hematologic effects of acute asphyxia in the normal and splenectomized dog, the splenic origin of asphyxic polycythemia, and so forth; (2) the contractions of the spleen during exercise and the results produced; (3) the contraction of the spleen following hemorrhage and the paradoxical polycythemia following a small hemorrhage; (4) the splenic reservoir during digestion, and the excito-motor effect of secretion on the spleen; (5) splenic contraction following emotion and the stimulation of sensory nerves; (6) the blood of the splenic vein and the capacity of the splenic reservoir; (7) the histophysiology of splenic contraction; (8) the humoral and nervous mechanisms of splenic contraction. The results confirm and in some cases amplify Barcroft's elucidation of this one of several functions of the spleen.

E. K.

Practical Massage and Corrective Exercises. By Hartvig Nissen. Pp. 271; 72 illustrations. Fifth edition. Philadelphia: F. A. Davis Company, 1929. Price, $2.50.

The subject matter of this volume is treated in a rather unscientific manner. The technique is antiquated, and the description of the physiologic effects of the various manipulations is frequently at variance with modern physiologic thought. The book, in typical pseudoscientific fashion, abounds in extravagant claims and boastful statements.

J. N.

BOOKS RECEIVED.

NEW BOOKS.

The Medical Record Visiting List or Physicians Diary for 1931, Revised. New York: William Wood & Co., 1930. Price, $2.00.

Pioneers of Public Health. By M. E. M. Walker, with Foreword by Sir Humphry Rolleston, Bart., G.C.V.O. Pp. 270; illustrated. London and Edinburgh: Oliver & Boyd, 1930. New York: The Macmillan Company. Price, 12/6.

Monographs on Biochemistry. Edited by R. H. A. PLIMMER, D.Sc., and SIR F. G. HOPKINS, M.A., M.B., D.Sc., F.R.S. *Bacterial Metabolism.* By MARJORY STEPHENSON, M.A., Associate of Newnham College, Cambridge. Pp. 320; 34 illustrations. London: Longmans Green & Co., Ltd., 1930. Price, 18s. net.

The Surgical Clinics of North America, Vol. 10, No. 5 (Pacific Coast Surgical Association Number, October, 1930). Pp. 71; 136 illustrations. Philadelphia: W. B. Saunders Company, 1930.

A Text-book of Gynecology. By ARTHUR HALE CURTIS, M.D. Pp. 380; 222 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $5.00.

A Brief History of Medicine in Massachusetts. By HENRY R. VIETS, M.D. Pp. 194; 8 illustrations. Boston: Houghton Mifflin Company, 1930.

Legal Medicine and Toxicology. By RALPH W. WEBSTER, M.D., PH.D. Pp. 862; 47 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $8.50.

The Relations of Psychology to Medicine and the Recognition and Treatment of Commoner Affective Disorders. By LEWELLYS F. BARKER, M.D., LL.D. Pp. 68. Lawrence, Kansas: University Extension Division, University of Kansas, 1930.

The Treatment of Children's Diseases. By PROF. DR. F. LUST. Authorized Translation of the Sixth German Edition with additions by SANDOR A. LEVINSOHN, M.D. Pp. 513. Philadelphia: J. B. Lippincott Company. Price, $8.00.

Practical Treatise on Diseases of the Digestive System, Vols. I and II. By L. WINFIELD KOHN, M.D., F.A.C.P. Pp. 1125; 542 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $12.00.

Intestinal Toxemia. Biologically Considered. By ANTHONY BASSLER, M.D., F.A.C.P. Pp. 433; 16 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $6.00.

Annals of Roentgenology, Vol. XII. Edited by JAMES T. CASE, M.D. *The Chest in Children.* By E. GORDON STOLOFF, M.D. Foreword by BELA SCHICK, M.D. Pp. 432; 401 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $15.00.

NEW EDITIONS.

A Text-book of Practical Therapeutics. By HOBART AMORY HARE, B.Sc., M.D., LL.D. Pp. 1104; 145 illustrations. Twenty-first Edition. Philadelphia: Lea & Febiger, 1930. Price, $7.50.

The continued demand for this popular book is ample evidence of the satisfactory way in which it provides for a widespread need.

A Primer for Diabetic Patients. By RUSSELL M. WILDER, M.D. Pp. 138; 2 illustrations. Fourth Edition. Philadelphia: W. B. Saunders Company, 1930. Price, $1.50.

A Text-book of Physiology. By WILLIAM H. HOWELL, PH.D., M.D., SC.D., LL.D. Pp. 1099; 308 illustrations. Eleventh Edition. Philadelphia: W. B. Saunders Company, 1930. Price, $6.50.

Developmental Anatomy. By LESLIE BRAINERD AREY. Pp. 563; 532 illustrations. Second Edition, reset. Philadelphia: W. B. Saunders Company, 1930. Price, $6.50.

A Text-book of Medicine. By RUSSELL L. CECIL, A.B., M.D., SC.D. Associated Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E. Pp. 1592. Second Edition. Philadelphia: W. B. Saunders Company, 1930. Price, $9.00.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Treatment of Malaria, With Some Reference to Recently Promoted New Remedies.—Bass (*J. Am. Med. Assn.*, 1930, **95**, 988) writes that quinin is the only specific remedy for malaria. It is possible that arsenic, acetarsone and plasmochin may have some effect, but he states emphatically that there is no reason whatsoever to employ these drugs when there is already a specific, taking of which does no harm, whereas with the other drugs direful effects are occasionally observed.

The Subsequent Course and Prognosis in Coronary Thrombosis.—Conner and Holt (*Am. Heart J.*, 1930, **5**, 705) have analyzed 287 cases of coronary occlusion in order to present statistical information concerning some of the features of this relatively common condition. They found that 85 per cent of the patients were men and it was essentially a disease of the fifth decade of life, the first attack occurring in one-third of all the cases before the fifty-first year and in three-fourths of the cases before the sixty-first year. Antecedent arterial hypertension occurred in approximately one-third of the patients, syphilis in one-eighth and diabetes in one-tenth. Of the 287 patients, 117 are known to be living and 142 to be dead, death occurring in the first attack in one-eighth of the cases. Of these patients who recovered, 75 per cent were in good health at the end of a year, 56 per cent at the end of two years, 21 per cent at the end of five years and 3.4 per cent at ten years. In almost two-thirds of the patients the attack occurred without antecedent circulatory symptoms in individuals who had had no subjective or objective symptoms of heart disease. A single attack was the usual story of these patients; two attacks occurring in only 24 per cent, three attacks in 4 per cent and four to seven attacks in 5 per cent. The interval between the attacks in those who had more than

one attack in 50 per cent of patients was less than a year. In the other instances the time period varied from one to eighteen years. The authors note that the immediate mortality is higher when the initial symptoms are severe than when they are mild, yet nearly one-third of the patients who survived had symptoms of a very severe character.

Studies on a Case of Sickle-cell Anemia.—The occurrence from time to time in the blood of negroes of a peculiar bizarre sickle shaping of the erythrocytes has occasioned considerable interest in the how and why of this familial condition. Hahn and Gillespie showed in 1927 by *in vitro* experiments that the phenomenon apparently depended upon oxygen tension and they suggested that the sickle formation might be brought about *in vivo* by conditions of anoxemia. SHRIVER and WAUGH (*Canad. Med. Assn. J.*, 1930, **13**, 375) presents a case observed in Canada. They demonstrate that the number of sickle cells in the peripheral blood may be altered by changes in the partial O_2 pressure. They note that the sickling takes place when the O_2 pressure falls below 45 mm. Hg. This they believe explains the occurrence of very large numbers of sickle cells in organs examined postmortem and likewise in spleens which have been removed after clamping the vessels of the pedicle. Because of the ability of the cells to take these unusual shapes in the blood stream and to return to normal when the O_2 pressure is increased, the authors indicate their belief that the disease is not primarily one of the spleen or of the bone marrow, but it is due to "an inherited property of the red cells which follows the Mendelian law and is peculiar to the negro race."

SURGERY

UNDER THE CHARGE OF

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Result of Treatment by Autogenous Gland Filtrate in Hodgkin's Disease.—HANROBAN (*Ann. Surg.*, 1930, **92**, 23) says that 9 patients who had Hodgkin's disease were treated by the immunologic method suggested by Wollhauser and Whitehead. This treatment consists in the frequent administration of small doses of a diluted filtrate, the extract of affected lymph nodes. Five died of the disease, 3 of whom had transitory remissions. One seemed unaffected by the treatment and returned to irradiation. One seemed very slightly improved for a time, but retrogressed and was irradiated. One was apparently unaffected after ten weeks and another after six weeks. These results are not clear enough to indicate whether or not the filtrate treatment has any appreciable effect on the usual course of Hodgkin's disease. Four cases suggest that it may be instrumental in bringing on a remission. Should the experience of others confirm this, it is to be hoped that this treatment will be given an extensive trial, preferably with no other treatment but if conditions demand, combined with irradiation.

Hereditary Deforming Chondrodysplasia.—Hyndman (*Arch. Surg.*, 1930, **21**, 12) says that the so-called malignant degenerative lesions in skeletons presenting hereditary deforming chondrodysplasia are probably all chondromatous. A chondroma developing in a skeleton showing hereditary deforming chondrodysplasia is essentially the same pathologic process as the nonhereditary chondroma and should be regarded in the same light. Although such chondromas are essentially benign, they should, in view of their vessel invading and metastasizing propensities and rapid expansive growth, be totally excised as early as possible. Therefore, it is incumbent on the surgeon to make a check-up examination at intervals when he has diagnosed hereditary deforming chondrodysplasia. Roentgenotherapy probably has no beneficial effect in this type of tumor. The definite ringlike foci in which the calcium is deposited in the tumors, particularly in the absence of bone destruction, is adequate evidence on which to make a diagnosis of osteochondroma. The marked deformity and foreshortening of either or both of two juxtaposed bones in hereditary deforming chondrodysplasia is probably due to pseudojoint formation and distorted stimulus of bone growth.

The Preoperative and Postoperative Therapeutic Use of Dextrose.—Titus (*Am. J. Surg.*, 1930, **8**, 1196) believes that the preoperative and postoperative administration of dextrose is now regarded as of great importance in the general care of the surgical patient. Intravenously injected dextrose will frequently convert the bad surgical risk into a comparatively safe surgical venture. Administered preoperatively by mouth or by vein, as necessity may require, it acts as a preventive of postanesthetic nausea, vomiting and acidosis. Routine postoperative intravenous injection of hypertonic dextrose solution is recommended in the prevention of vomiting, acidosis and shock, intestinal atony, etc. Dextrose solution injected intravenously is effective supportive treatment for traumatic shock, peritonitis and the toxemia of intestinal obstruction. Modes of administration, dosage and indications for dextrose therapy are discussed in this paper. The assertion is again made that unfavorable reactions from intravenous injections of dextrose are avoidable if certain technical but simple essentials are understood and observed by the operator.

Actinomycosis of the Thorax.—Good (*Arch. Surg.*, 1930, **21**, 786) declares that the symptoms of actinomycosis of the thorax may simulate those of bronchitis, bronchopneumonia, pulmonary abscess and pulmonary tuberculosis. The more common symptoms are fever, cough, sputum, pain, weakness, loss of weight, dyspnea, anemia and external abscesses. The diagnosis of actinomycosis is made by demonstrating the sulphur granule in the sputum, in empyema fluid or in the pus from an abscess or by demonstrating the actinomycotic lesion in a histologic specimen. Treatment should be directed at improving the general health, the administration to tolerance of potassium iodide, the drainage of abscesses and empyema pockets and the proper use of Roentgen ray and radium. The disease is fatal in from 60 to 70 per cent of the cases.

The Problem of Early Genital Lesions.—Wenger and Proske (*Am. J. Syph.*, 1930, **14**, 313) say that their experience has proved that the differential diagnosis of the two lesions (chancre and chancroid) is possible by repeated examinations and careful observations in 86 per cent of the cases studied. In the remaining 14 per cent of this series, the diagnosis remains in doubt, because all of the patients were transient, not sufficiently intelligent to realize the importance of the six months' period of observation. The authors believe that the general practitioner would be justified from the standpoint of public health to regard all early genital lesions, as probably chancre, where he has no proper facilities for making a differential diagnosis, since the criterion for the diagnosis of chancroid is impracticable except in a few cases. The greatest good to greatest number can be accomplished only by early treatment and that it is safer to treat a possible case of chancroid as syphilis, rather than permit a chancre to pass as chancroid. Except in very rare instances and where the patient is under perfect control, should the physician wait for possible later manifestations of syphilis, since they are always uncertain. If all cases of early penile lesions were treated as early syphilis, we would prevent many new infections and a great deal of latent syphilis.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Progressive Muscular Dystrophy with a Combination of Adrenalin and Pilocarpin.—On the basis of his own earlier proof that progressive muscular dystrophy rests upon a disturbed autonomic innervation of the muscles, Ken Karé and Shigeo Okinaka (*Klin. Wchnschr.*, 1930, **9**, 1168) report the results of an effort to control or improve this disease by the prolonged administration of adrenalin and pilocarpin. They had previously shown that subcutaneous injections of adrenalin and of pilocarpin, separately or combined, increased the function of the dystrophic muscles. They had, further, evidences that in animals the continued stimulation of autonomic muscle innervation produced hypertrophy of the stimulated muscles. On the basis of these findings they administered subcutaneous doses of 0.2 to 0.3 cc. of 1 to 1000 adrenalin solution and 0.1 to 0.2 cc. of 1 per cent solution of pilocarpin daily or every other day for fifty or more consecutive injections. Twelve patients were treated by this method and a pronounced

increase in the strength of the affected muscles was observed in from two to three hours and lasted twelve hours on the average. After from 15 to 30 injections most patients showed a lasting increase in the strength of the muscles which frequently persisted for many months after cessation of the injections. Two patients showed almost complete recovery with relief of symptoms. So great was the recovery that they might almost be classed as cured. Six others showed pronounced improvement. A few showed almost no effects. The authors observed that, if there was little or no benefit after a series of 50 injections, the outlook for ultimate benefit was extremely unfavorable, while those patients showing some definite improvement could be further restored by continuation of the treatment. Although the injection is frequently followed by some mild tachycardia and palpitation of the heart, this is of brief duration and no ill effects could be observed. Neither cardiac hypertrophy nor persistent elevation of the blood pressure was observed in any patient. Even in those patients in whom there was no marked improvement in muscle tone or strength, it was generally observed that the treatment checked the progress of the disease. The authors refuse to regard the treatment as a cure but believe that it offers the best prospects for checking the progress and reducing the severity of progressive muscular distrophy so far available.

The Influence of Digitalis on the T Wave of the Electrocardiogram.—Blumenfeldt and Strauss (*Zeitschr. f. klin. Med.*, 1930, **113**, 502) have reinvestigated the question of reduction in the amplitude of the *T* wave or of inversion of this wave by digitalis as an objective sign of its therapeutic action. This reinvestigation was prompted by recent reports by Brams, who failed to confirm the constancy of this sign. The authors found, in a series of carefully controlled experiments on rabbits in which varying doses of digitalis in the form of digipuratum (digitan) were employed to produce either acute or chronic digitalization, that the previously positive *T* wave could not be inverted to a negative wave in a single animal. In three of their animals the *T* waves however were somewhat reduced in amplitude. They studied in a similarly carefully controlled manner a series of 40 patients employing several different preparations of digitalis including digitan. In only one of this entire series was there any significant change produced in the *T* wave which, in this case, in Lead 2 changed from an originally diphasic wave to a negative wave. On the other hand, the amplitude of the positive *T* waves increased in many of their cases. In approximately two-thirds of all the patients the *T* waves remained practically unchanged. They concluded that the changes in the *T* waves originally described by Cohn (inversion) and Pardee (reduction in amplitude) as evidences of the therapeutic effect of digitalis in man cannot be accepted as trustworthy.

Investigations on the Absorption of Calcium from the Gastrointestinal Tract.—Dr. Erich Hesse (*Klin. Wchnschr.*, 1930, **9**, 1358) calls attention to the fact that the absorption of calcium is not dependent upon the solubility in water of the preparation used, the form in which it is absorbed finally being a complex calcium soap, not an ionizable salt. Its absorption seems to depend largely upon the hydrogen-ion concen-

tration of the intestinal contents. When this is well on the acid side of neutral the absorption of calcium takes place. The absorption can therefore be controlled in large measure by the selection of a diet yielding an acid reaction in the intestinal tract. For this purpose a diet containing large quantities of lactic acid is specially favorable, although milk itself leads to alkalinity of the intestinal content. Carbohydrates on the other hand, even when combined with a milk diet, cause acidity and promote calcium absorption. The author reports a series of careful, quantitative studies carried out on dogs, in which he used an insoluble calcium-potassium preparation prepared from animal bones, and containing a vitamin, known as Pro-Ossa. He found, when the animals were on a mixed diet, that two-thirds of the administered calcium was absorbed within twenty-four hours. The same results were obtained in dogs fed exclusively with carbohydrates. However, when the dogs were fed with cow's milk only one-tenth of the administered calcium and a third of the phosphorus was absorbed. However, the administration of large doses of lemon juice or milk sugar, even in the presence of a milk diet was capable of greatly increasing the absorption of calcium. Also, if the calcium preparation were administered continuously for ten days along with either milk or a mixed diet satisfactory absorption of calcium took place, indicating that it was capable of more than neutralizing the alkaline reaction in the intestinal content.

PEDIATRICS

UNDER THE CHARGE OF

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Suspected Juvenile Tuberculosis.—EBERSON DELPRAT and WOLFF (*Am. J. Dis. Child.*, 1930, **40**, 753) made a clinical and roentgenologic study of 306 cases of suspected juvenile tuberculosis with special reference to the evaluation of 9 clinical symptoms, 10 clinical signs, 9 Roentgen observations and the tuberculin test. Two groups of children were selected on the basis of their reaction to tuberculin. In the positive group which comprised 206 patients, no symptoms were presented in 36.4% as compared with 42% giving no symptoms among the negative group of 100 patients. The symptoms that occurred most often in both groups were cough (41.8%) in the positive and 55.2% in the negative, and nervousness (41.8%) in the positive and 39.6% in the negative. The differences between the percentages of total occurrences of symptoms in both groups were never greater than 7%, except in the case of cough, which in the series of patients with negative reactions exceeded those with positive reactions by 13.4%. Considering symptoms occurring in combination with others, it was found that none exceeded a difference in percentage of 5.5%, the greatest differences being in favor of the persons with positive reactions in connection with loss of weight

or failure to gain and nervousness. It was found that in the tuberculin-positive group 11.2%, and in the tuberculin-negative group that 12% presented no clinical observations. One sign occurred 6.3% more often in the positive group, but otherwise there were no appreciable differences in percentage. Two observations occurred most frequently in both groups (39% in the negative and 35% in the positive). Three observations were next in order (25% in the negative and 23.8% in the positive group. In all of these instances the negative exceeded the positive group. The percentage of patients in the positive group giving histories of one or more clinical symptoms was 88.8 and in the negative group, 88%. The percentage distribution of the total number of cases in which a clinical symptom or sign occurred alone or in combination with others was as follows: In the positive group, malnutrition, dullness over the manubrium and enlargement of the cervical lymph glands occurred more often: while D'Espine's sign, paravertebral dullness and auscultation exceeded among those with negative reactions. The greatest difference was in favor of the negative group in the case of paravertebral dullness. No roentgenologic evidence was found in 5.8% in the positive group and in 15% in the negative group. The percentage distribution of the total number of cases in which roentgenographic signs occurred alone or in combination with others was as follows: In the positive group, hilus calcifications, increased bronchial markings and thickened interlobar pleura occurred more often: in the negative group, peribronchial infiltration occurred more frequently; and the other roentgenographic signs occurred approximately in the same percentage in both groups. Certain outstanding physical evidences, such as D'Espine's sign, paravertebral dullness and the like were more prevalent among persons with negative tuberculin reactions. Observations that were formerly considered as pathognomonic of tuberculosis were associated with nontuberculous processes in the lungs. The authors found that commonly accepted clinical symptoms and signs have no diagnostic significance unless these are definitely correlated with tuberculin tests and Roentgen observations that are positive for tuberculosis.

Intraperitoneal Therapy in the Treatment of Diseases of Children.—GRULEE (*Penna. Med. J.*, 1930, **34**, 71) grouped the dangers of intraperitoneal therapy under three heads: infection, excessive quantity and untoward reaction. Infection may be introduced from improper or insufficient sterilization of the skin, instruments, or materials injected. This would seem a remote possibility if proper care is used. Peritonitis might develop as a result of puncture of the bladder or intestine. There is a real danger of metastatic infection in the peritoneal cavity from infection elsewhere in the body, especially following an intraperitoneal transfusion of blood. Too large quantities may result in pressure on the diaphragm with resulting syncope especially if there is abdominal distention present. Reaction of an untoward nature may follow injections, especially if care is not exercised in the preparation of the material to be injected. Such reactions usually consist only of slight rise in temperature and distention. At times the reaction is much more serious

with collapse and in rare instances, death. The disadvantages are chiefly those of somewhat delayed absorption. This is especially evident with red corpuscles. The material injected usually is rapidly absorbed. The rate of absorption varies with the condition of the patient, but it is usually rapid. The greatest barrier that has to be overcome is the psychical one, that is the result of our surgical training. The advantages are obvious if the cases are properly selected. Oral and rectal administration is often quite ineffective when their ingestion is most needed, and the supply that can be given subcutaneously or even intravenously is often entirely inadequate to meet the demands. In many cases of anemia any therapy except transfusion of blood is of no avail and should this have to be repeated often as is frequently the case, the intravenous route is impossible and the intraperitoneal must be used. There are two distinct advantages. The reactions are certainly fewer and slighter than in intravenous injections, and the simplicity of the procedure is such as to make it applicable for almost universal use.

Studies in Infant Nutrition: Lactose and a Maltose-dextrin Preparation.—GERSTLEY (*J. Am. Med. Assn.*, 1930, **95**, 1233) states that chemical studies have shown that lactose *per se* does not deserve its bad reputation. It can be given to a normal infant in good hygienic environment without undue risk, even with the additional digestive strain of whole cows' milk. If intestinal fermentation and diarrhea arise, they are not proportionate to the amount of lactose in the formula. Unquestionably some other element of cows' milk, probably by delaying lactose absorption, and thus permitting a greater total bacterial growth and increased fermentation, or by increasing peristalsis, plays a great rôle. The relation of lactose to protein seems important. In a former study the author indicated the very important part played by parenteral infection. Secondary in importance only to parenteral infection in influencing stool chemistry is the child's general nutrition. The amount of lactose in the diet is not nearly so important as the factors influencing its absorption. In regards to the maltose-dextrin preparation, the analyses of the stool showing low total and lactic acids and hydrogen-ion concentration toward the alkaline confirm the clinical observations of its constipating tendency. When given to the normal infant in a mixture of cows' milk, it results in changes in stool chemistry further from that of the breast fed than does lactose. Whether the success of lactic acid milk is due to the lowering of the buffer, or whether the fine curd is a factor, in either case the theory of the success of the method is in its digestibility. He found that whole cows' milk with carbohydrate seemed to effect a change in the infant's body predisposing to severe nutritional disturbances, and causing him to show the severest nutritional reaction following the mildest parenteral infections. These changes were independent of any gastrointestinal disturbance. The addition of lactic acid to milk may make the mixture more digestible, but does not take away any of the factors which were found to injure the body.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Diagnosis and Treatment of Scabies.—MONTGOMERY and CULVER (*Med. J. and Record*, 1930, **132**, 337) in discussing the accepted clinical features of scabies mention a number of less well-known facts which assist in the diagnosis of this common dermatosis. They state that the characteristic elementary lesion of the disease, the burrow, is best seen on the anterior aspect of the wrists and the adjacent palms rather than on the sides of the fingers. The burrow is almost never identified on the tips of the elbows, the areolæ of the nipples, or over the buttocks. It is frequently discoverable, however, on the glans penis and in infants on the tender skin of the instep. The burrow may frequently be demonstrated by placing on the suspected part a drop of ink or iodin which is instantly wiped away. A minute amount of the substance ascends the burrow by capillary attraction, bringing the latter into better relief. The authors believe that an automobile age accounts for a greater prevalence of the disease by markedly increasing the number of transient overnight guests at hotels, inns and wayside homes. Auto drivers are apt to have extensive involvement about the buttocks from constant sitting with the attendant warmth of the parts. The motorist may escape much involvement of the hands, however, because of frequent contact with gasoline, which is inhibitory to the life cycle of the itch mite. In discussing the characteristic itching of scabies, they call attention to the fact that the glans, though a favorite site of involvement, rarely if ever itches. The question is raised if this is not due to the glans being covered by a mucous membrane. The analogy to lichen planus is mentioned, for when this disease affects the oral cavity there is no itching despite the fact that cutaneous lesions are very pruritic. The authors state that occasionally scabies may be non-pruritic throughout its entire course and recite the case of a scabies carrier who over a period of sixteen years had infected many people and whose house came to be shunned. The diagnosis of scabies was established by demonstrating the mite, yet there had been no itching throughout the protracted course of the infection.

The Kidney Function in Pemphigus.—AYRES (*Calif. and West. Med.*, 1930, **33**, 556) has studied the kidney function in 8 cases of pemphigus by means of the phenosulphonephthalein test. All showed decreased excretion of the dye ranging from 5 per cent output in two hours after

giving the drug intramuscularly, to 55 per cent output in one hour after intravenous injection. On the basis of these findings, plus citations in the literature calling attention to postmortem evidence of pathology in the liver in certain cases of pemphigus, the author cautions against the administration of arsenic in this disease. He believes that an extensive case of pemphigus is comparable to a severe burn with the attendant fluid loss by exudation and therefore advises a copious fluid intake fortified by parenteral administration if swallowing is difficult.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Urinary Incontinence in Women.—One of the most annoying conditions affecting many women is urinary incontinence due to relaxation or rupture of the internal vesical sphincter. Such women may have perfect control of the bladder under ordinary circumstances but under the stress of unusual exertion or excitement they become incontinent. In the severer forms, operative intervention is all that the gynecologist can offer. In a consideration of the surgical treatment, SMITH (*Ann. Surg.*, 1930, **92**, 394) states that he has found that a careful plastic repair of the anterior vaginal wall will correct the impaired bladder control in the majority of instances. In more pronounced cases, the Kelly operation of tightening the vesical sphincter combined with colporrhaphy gives a cure in a considerable proportion of women with relaxed sphincter. In a case of his where this procedure failed, the addition of suprapubic bladder drainage to the plastic on the sphincteric region supplemented by an interposition operation gave an excellent result. While such a procedure may seem a bit radical to the gynecological surgeon, it should be remembered that the urologists consider suprapubic bladder drainage as a minor addition to any operation and it is certainly well worth while to keep such an aid in mind, since the rest which is allowed the bladder by this means may be the difference between success and failure when attempting to correct extensive degrees of vesical incontinence.

Relation of Histology to Prognosis in Cervical Cancer.—In an effort to determine the degree of malignancy so that the prognosis could be given, MCNAMARA (*J. Lab. and Clin. Med.*, 1930, **15**, 976) studied 294 cases of carcinoma of the cervix and found that the microscopic examination is one of the most valuable assets in this determination. The squamous-cell type of cancer was divided into two types of malignancy,

which he calls "high" and "low." The "low" group is made up entirely of large even cells, which have a tendency toward "pearl" formation. The cells as a rule are equal in size and do not infiltrate. The "high" group is made up of spindle cells, with much chromatin and a small nucleus. They are closely packed, giving the appearance of the ordinary basal-cell carcinoma. This is the highest or most malignant type of cancer found. Along with this squamous cell there is usually a round cell with a clear cytoplasm and a very early chromatinized nucleus, which never invades the tissues. He has no accurate data on adenocarcinomas, having had only 3 cases. This report is of interest in view of the numerous reports from different investigators during the past few years. Some of the reporters place great importance on the histologic structure as a prognostic index, while others have failed to note any definite connection between the two, so that from the standpoint of the Reviewer, this subject must be considered to be in an unsettled state.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Oculogyric Crises in Postencephalitic States.—BENNETT and PATTEN (*Arch. Ophth.*, 1930, **4**, 361) reported 7 typical cases representing the syndrome of oculogyric crises, postencephalitic. In 6 patients modified Parkinsonian residuals were present, but a seventh patient was not Parkinsonian. The spasmodic conjugate deviations of the eyeballs was present in all. In addition most of the patients presented the symptoms of involuntary, forced closure of the eyelids with blepharospasm. The conjugate deviation was rather constantly accompanied by fluttering or flickering of the lids. Various therapeutic measures were tried but no definite improvement was seen except in the use of continuous medication with hyoscine or stramonium, which usually gave some relief. One patient improved markedly with general constitutional treatment and the administration of hyoscine. Tincture of stramonium in physiologic dosage gave no additional palliative relief from the attacks over the hyoscine, but in some instances apparently relaxed the bradykinetic tendency more strikingly than hyoscine. Both of these drugs are much worth while and should be administered; they often permit a completely incapacitated patient to return to work. No tendency to spontaneous cure was noted in these cases.

The Blood Picture in Keratomalacia of Adults.—ARNOLD and YOUNG (*Arch. Ophthal.*, 1930, **4**, 309) studied the blood picture of 35 patients with keratomalacia. In 7 the anemia was closely associated with the keratomalacia for no other cause was found. In 8 others the anemia could be explained on the basis of infectious disease, such as tuberculosis, kala-azar, empyema and paratyphoid fever. Others, however,

were suffering from advanced infectious diseases but did not have anemia. It is not known whether anemia can be produced by deficiency of vitamin A alone, but in 7 cases in which no general disease was found responsible for the anemia there was no deficiency of vitamins B, C, and D, or at least it was not recognizable. "When keratomalacia has progressed to a far-advanced stage and has been further compliplicated by intercurrent infections, a state of serious disturbance in nutrition is obviously present. Anemia in these cases is usually marked. On the other hand, in cases in which the ocular lesion is mild and other complicating factors are absent, there is no appreciable change in the blood picture."

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Bacteria of the Upper Respiratory Tract and Middle Ear of Albino Rats Deprived of Vitamin A.—It has been shown by the researches of Werkman[1] and others that in the experimental animal a deficiency of vitamin A increases susceptibility to infections, especially respiratory infections; and that this cataphylaxis in animals is not the result of the destruction or paralysis of the antibody-forming mechanism that produces agglutinins, precipitins, hemolysins or bacteriolysins but of a depressive agent acting upon the phagocytic mechanism. Barlow,[2] too, has noted inflammatory changes in the upper respiratory tract in rats deprived of vitamin A. More recently, TURNER, ANDERSON and LOEW (*J. Infect. Dis.*, 1930, **46**, 328) report a bacteriologic study of the nasal cavities and middle ear in 79 albino rats, some of whom received a vitamin-A-free ration. Four types of bacteria pathogenic to rabbits were encountered: Staphylococcus aureus, B. coli, and two Gram-negative cocci—M. catarrhalis-A and chromogen-6. It was found that the pyogenic Gram-negative cocci occurred more frequently in those rats presenting the severest symptoms of vitamin-A deficiency. This the authors believe to be due to a depressed state of the experimental animal resulting from avitaminosis A. Evidence is produced to show that cod-liver oil protects against bacterial invasion of the nasal cavities and middle ear.

Occurrence of Influence Bacilli in Mouths of Normal People.—By employing penicillin in the isolation of hemoglobinophilic bacilli, FLEMING and MACLEAN (*Brit. J. Exper. Path.*, 1930, **11**, 127) were able to obtain influenzal and para-influenzal bacilli from the gums of all of 30 healthy nurses and students and of 6 healthy laboratory workers. Practically all of the cultures from the tonsils and naso-

[1] *Vide* Retrospect: J. Infect. Dis., 1923, **32**, 247.
[2] *Vide* Retrospect: AM. J. MED. SCI., 1929, **178**, 290.

pharynges in the series of 30 yielded similar bacillary forms. Although the hemoglobinophilic microörganisms varied considerably in their morphologic and tinctorial characteristics, most of them were non-hemolytic. In another series of cultures from the apices of infected teeth 3 out of 4 revealed hemoglobinophilic bacilli.

RADIOLOGY

UNDER THE CHARGE OF

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Further Observations on the Direct Roentgenologic Signs of Gastrojejunal and Jejunal Ulcer.—The direct roentgenologic signs which, according to CAMP (*Radiology*, 1930, **15**, 274), permit a positive diagnosis of gastrojejunal or jejunal ulceration are: (1) The presence of an ulcer niche; (2) persistent deformity of the stomach, stoma or jejunum; (3) the presence of a gastrojejunocolic fistula, and (4) closure of the stoma. These conditions are best shown during the fluoroscopic examination with the patient upright. The stomach should be empty and the examination should begin after only a swallow or two of the opaque meal. It is Camp's impression that a niche will be seen in about 60 per cent of the cases. The majority are found in the jejunum, nearly always in the efferent loop and sometimes as far as 15 cm. from the stoma. Usually the shadow of the niche is less than 1 cm. in diameter and projects from the lateral border of the efferent loop, frequently close to the stomach. Occasionally it is situated within the stoma. It must be distinguished from flecks of barium caught in the gastric rugæ or jejunal folds. Deformity of the stomach, stoma or jejunum produced by the associated inflammatory reaction is the most common change accompanying gastrojejunal or jejunal ulcer. It appears as a puckering about the stoma or narrowing of the jejunum. Frequently the deformed stoma has a funnel-like appearance. In the absence of a malignant lesion, a gastrojejunocolic fistula is evidence of preceding jejunal or gastrojejunal ulceration, whether additional signs are present or not.

When Has Visceroptosis Clinical Significance?—To this question BEILIN (*Radiology*, 1930, **15**, 223) answers as follows: When symptoms arise as a result of perverted function in a visceroptotic individual in whom organic disease has been excluded, then, and then only, has visceroptosis clinical significance. The cardinal diagnostic fluoroscopic sign of gastroptosis and coloptosis is that the symptoms are usually relieved when the stomach or colon is elevated manually, and almost

immediately entirely relieved when the patient is placed in the Trendelenburg position. The anatomic position of the stomach and colon in the so-called normal individual is dependent upon the habitus as well at the inherited constitutional frame of the individual. Their low position is of no significance except when it interferes with physiologic function. The responsibility for the diagnosis of clinical gastroptosis and coloptosis is almost entirely dependent upon the clinical roentgenologist, as a careful objective exclusion diagnosis of organic disease of the gastrointestinal tract must be made.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Landry's Paralysis: A Clinical and Pathologic Study.—Golby (*J. Neurol. and Psychopathol.*, 1930, **11**, 1) presents 3 cases of Landry's paralysis which he has studied and data on 54 cases collected and tabulated from the literature. He divides these cases into three groups as follows: I. A form of acute ascending paralysis occurring almost exclusively in males, usually during the third decade of life, with 50 per cent mortality and slightly better prognosis prior to the age of thirty years. The paralysis is almost, but not quite always ascending in type; it is not associated with wasting, or with changed electrical reactions. Slight sphincter disturbance is not uncommon. Bulbar involvement is usual, but the nuclei of the upper cranial nerves are not as a rule affected. Sensory changes are almost entirely subjective, such as paraesthesiæ, pains, aching, numbness, and so forth, often preceding the onset of paralysis by a few days. Febrile reaction is conspicuous by its absence, nor are there any signs of meningeal irritation or of increased intracranial tension. Postmortem findings are limited to vascular engorgement of the meninges, chromatolysis in the cord and a few fatty changes in the nerve tracts and peripheral nerves, not of a specific nature. If recovery occurs, it is complete but may take a year or more. Fatal cases last about fifteen days and respiratory paralysis or bronchopneumonia are usually responsible for death. II. Differs from the foregoing in a smaller mortality and higher incidence in females but males predominate. The age incidence and prognosis is similar. Paralysis is almost always ascending. The motor cranial nerves are commonly involved, usually as symmetrically, and changed electrical reactions and wasting are sometimes seen. Sphincter disturbance is more frequent. Sensory changes are similar to those in Group I. Slight objective changes occur, in the nature of tenderness over nerve trunks

in about half the cases. Signs of a general toxemia are common, and there is more constitutional illness than in Group I. Postmortem changes in the cord and peripheral nerves are always present and of a parenchymatous nature, with or without inflammatory reaction. Recovery is often complete in two or three months but sequelæ, such as wasting and absent deep reflexes are not uncommon. Fatal cases last usually about fifteen days. III. Mortality high (80 per cent); age incidence low, as a rule under twenty years; males preponderate markedly; sequence of paralysis more variable and there is a tendency for the onset to occur in one limb. Bulbar involvement is common and is somewhat similar to Group I. Sphincter disturbance is more frequent than in either of the other two groups. There is a marked febrile reaction often associated with signs of increased intracranial tension and meningeal irritation. There is almost complete absence of sensory changes. Postmortem changes are similar to those of anterior poliomyelitis. Residuals in recovered cases are similar to those found for poliomyelitis. On the basis of these findings and comparing his view with those of previous writers he agrees with Saltman that cases of acute ascending paralysis can be divided into three groups; a poliomyelitic group, a polyneuritic group, and a group which shows little or no postmortem change and no constitutional reaction. These groups can be distinguished with a degree of certainty on clinical and pathological grounds. A high mortality and a preponderating incidence on young adult males are characteristic of the whole series. Although the cases fall into clinical and pathologic groups and may be described as diseases in the traditional manner, there is no common etiology. "Landry's paralysis is a syndrome probably caused by a toxin exerting its influence through the blood stream, and more or less closely related on the one hand to a group of cases which are simply a variety of multiple neuritis, and on the other to a group which are best described as cases of infective poliomyelitis."

Congenital Word-deafness, With Some Observations on the Accompanying Idioglossia.—Morrison (*J. Neurol. and Psychopathol.*, 1930, **11**, 28) presents 2 very interesting cases of congenital word-deafness occurring in the same family and with some evidence of auditory disturbance in still another member of the family. The cases are presented with sufficient detail to be illuminative. The evidence, as it appears, leads the author to the opinion that if the condition is due to a lesion of some anatomic entity, the cases presented shed no light on the cerebral localization of such a center. The evidence did point to a very great specialization in such a center if it exists. He suggests that the condition may be due to an unusual form of the functional harmony of the cerebral make up of the individual. He finds that the social handicaps, due to such a grave inherent condition, appear to depend for the most part on the general intelligence of the afflicted. He believes that the idioglossia manifestations may be due to a striving of the individual for speech production in the absence of any retention of word memory and in the presence of a partially developed lip-reading memory. As lip-reading becomes more efficient, the anomalies of speech decrease.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Changes of the Spleen in Subacute Bacterial Endocarditis.—Fox (*Arch. Path.*, 1930, **10**, 402) has studied the changes in the spleen in 25 cases of subacute bacterial endocarditis. The gross changes in the more rapidly fatal cases, consisted of moderate enlargement of the organ which was usually soft, purplish in color and possessing a thin, smooth capsule. In the cases of longer duration, the splenic enlargement was much more marked. The pulp in this later stage was firm and red: infarcts and perisplenitis were marked features. Microscopically hyperplasia of the lymphatic tissues was not evident at any stage of the disease. On the other hand, hyperplasia of the reticuloendothelial cells, though not seen early, was more marked in the later stages of the disease. In several cases, accumulations of cells were encountered, usually near bloodvessels. They consisted of cells with elongated nuclei of connective-tissue type, with a few large round mononuclears and an irregular scattering of polymorphonuclears. Polymorphonuclear neutrophils were also found scattered through the tissue singly and in groups. Evidence of the destruction of blood was seen only in the late stages of the disease, while involvement of the lining of bloodvessels was not an outstanding peculiarity.

Tissue Reactions in Rabbits Following Intravenous Injection of Bacteria.—Nye and Parker (*Am. J. Path.*, 1930, **6**, 381) have reported observations on the tissue reactions of rabbits following the repeated intravenous injection of relatively large doses of living and dead nonhemolytic streptococci. Dead cultures of various other organisms were also used. A marked reaction occurred in the lung, liver and spleen, while reactions of lesser degree were found in the bone marrow, kidney glomeruli and adrenal cortex. The reaction consisted of an accumulation of lymphoid cells beneath the endothelium of the finer veins in the lung and about the sinusoids of liver and spleen. These cells were eventually transformed into, or replaced by, monocytes and giant cells. The collections of cells were sometimes sufficiently large to almost obliterate the lumen of the vessel. Similar reactions were observed in tissues from animals which had received repeated injections of colloidal substances such as India ink and collargol. The lesions were of a temporary nature, disappearing in the course of some days after the last injection. The cellular responses were regarded by the authors as representing the reaction of the normal rabbit to foreign materials of certain varieties in the blood stream. The process was nonspecific and had no relation to sensitization or immunization.

Renal Lesions with Retention of Nitrogenous Products Produced by Massive Doses of Irradiated Ergosterol.—The kidneys of rabbits fed with massive doses of irradiated ergosterol were studied by SPIES and GLOVER (*Am. J. Path.*, 1930, **6**, 485). They were examined in detail histologically and the effect of the lesions upon kidney function, as determined by the retention of nitrogen products, was also observed. Some of the animals were killed early in the experiment while the remainder were allowed to die from the effects of the ergosterol. No gross changes were visible in animals which had received irradiated ergosterol for less than nine days, but in the more advanced cases, small deposits of calcium were studded over the cut surface of the cortex and sometimes deposits were visible also in the medulla. Some sclerosis of the renal arteries was observed in the animals showing gross deposits of calcium. The animals which lived longest showed the most advanced lesions. Histologically the arteries showed deposits of calcium in the media with hyalinization of the vessel walls in the neighborhood. Hyaline deposits and marked calcification were observed in the basement membrane of the kidney tubules and in the glomerular capsules, while pronounced atrophy of the tubular epithelium also occurred. The impairment of kidney function was in general, proportional to the amount of kidney damage as shown by histological examination. There was a retention of nitrogenous products in the blood accompanied by the appearance of large amounts of albumin in the urine. These effects were observed only during the last few days of life in those animals which died from the toxic action of the irradiated ergosterol.

A Clinical and Pathologic Study of Periarteritis Nodosa. A Report of 5 Cases, One Histologically Healed.—ARKIN (*Am. J. Path.*, 1930, **6**, 401) has studied the clinical and pathologic aspects of periarteritis nodosa and in this paper reported 5 cases of this disease. He regarded the affection as a specific infectious disease probably caused by a filtrable virus with an elective affinity for the arteries. Clinically, the chief signs were those of a septic temperature, polyneuritis and polymyositis, hematuria or nephritis, crampy abdominal pains and progressive emaciation. The pathologic changes were divided into four stages: (1) Alterative-degenerative; (2) acute inflammatory; (3) granulation tissue, and (4) histologically healed end-stage or scar-tissue stage. The first stage is marked by degeneration of the media, frequently without symptoms. In the second stage the media becomes involved in an acute exudative inflammatory reaction which extends into the intima, and adventitia. In this stage the typical symptoms appear. In the stage of healing and the final healed stage the clinical symptoms depend upon the location and degree of damage to the vessel walls. One of the cases reported fell into the fourth class or healed end-stage. This patient came to autopsy four years after a single severe illness marked by icterus, high fever and acute nephritis. The cause of death was renal and cardiac insufficiency. Histological examination of the arteries revealed the healed stage of periarteritis nodosa. The author considered complete healing a rare occurrence, and emphasized the importance of microscopic examination of the arteries of organs which show atrophy or extensive fibrosis, in order to detect the healed lesions.

Basal-Cell Carcinoma. A Study of 836 Cases.—Owen (*Arch. Path.*, 1930, **10**, 386) has reported the result of histologic examination of the tissues removed at operation from 836 cases diagnosed as basal-cell carcinoma. Of these cases, 718 proved to be simple basal-cell carcinoma; 111 were basal cell and squamous cell mixed; while 7 were pigmented basal-cell carcinoma. In this series, not one case was found in which a true basal-cell carcinoma had originated in mucous membranes. Microscopic examination of an additional series of tissues removed at biopsy from mucous surfaces in more than 500 cases, also failed to reveal a single case of true basal-cell carcinoma. The author emphasized this point and indicated that the disease is primarily one of the skin, occurring in a large percentage of cases in the skin of the face and head. Similar lesions occurring in mucous membranes were found to possess more invasive qualities, and careful microscopic examination usually showed them to be carcinomata of squamous-cell type.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Effect of Local Ultraviolet Radiation on Resistance to Infection: Bacillus Leptisepticum Abscesses in the Rabbit.—Chapman and Hardy (*Am. J. Hyg.*, 1930, **11**, 404) have carried out studies in the hope of obtaining some experimental evidence of the effect of ultraviolet radiation on resistance to infection. With the exception of one case, all the evidence collected goes to show that local radiation, in light, moderate, or heavy doses, single or repeated daily for two weeks, has no effect in preventing or mitigating the lesions produced by subcutaneous implantation of Bacillus lepisepticum. It is possible that the effect of the ultraviolet light, which is known to penetrate the skin very slightly, may be less marked on an organism introduced subcutaneously than on one which must make its own way through the skin, or parasitize the cells of the skin itself. Also, it is conceivable that better results might be obtained by using smaller doses of bacteria, but it was desired to eliminate the element of chance. Radiation, with just the right timing and dosage, may have some effect in turning the balance in favor of resistance, but this result is indeed difficult to attain. The conclusion drawn from these experiments, if any is justified, is that local radiation in light doses does not enhance the resistance of rabbits to subcutaneous infection with Bacillus lepisepticum, and that, in very heavy doses, it may be harmful.

Cancer Death Rates, Smoke and Topography.—MEYERS (*Am. J. Pub. Health*, 1930, **20**, 581) states that there is a variation in cancer death rates between countries, states, cities, even adjacent, and very probably between parts of cities. Green's work in England and Scotland and Bertillon's figures for France would seem to point to a distinct influence of topography and of combustion products of fuel on cancer death rates. The Staten Island cancer study along the lines of Green's theories, but allowing for age, sex, nativity, nationality, diet, allocation, exclusion of institutional deaths, and a three-year period of residence before death, points to a relationship between smoke and fumes from industrial plants and homes and topography and cancer prevalence. Other statistical, chemical, and experimental data point to the influence of smoke and fumes or tar on cancer. What the action and nature of a cancerogenic factor liberated by combustion are is not certain. Whether such factor is chemical or possibly radioactive in nature is material for other studies. Further studies like the Staten Island investigation should be made by city, county, state or national health bodies, or cancer organizations. This means a corps of experts in a number of fields. The burden of such a study is too great for a single worker. Further studies are now indicated and offer a rich field for an advance in the knowledge of the etiology of cancer in the case of (1) Minneapolis and St. Paul, (2) San Francisco and Oakland, (3) Albany, N. Y.

Influence of Age Upon Antibody Formation.—Immunity conditions in young animals have long been investigated very extensively. Most of these studies have been concerned with the transmission of antibodies from the mother to the offspring with the blood through the placenta and by the milk. Comparatively little work has been done on the subject of antibody formation in young animals. Yet it is obvious that antibody formation in young animals is an important factor in their resistance to certain infectious diseases, in their behavior in the phenomenon of hypersensitiveness, and in their capacity to be actively immunized with toxin-antitoxin mixtures, anatoxin and vaccines. FREUND (*J. Immunol.*, 1930, **18**, 315) reports experiments which show that in rabbits less than twenty days old the formation of agglutinins against typhoid bacilli, of hemolysins against sheep cells, and of precipitins against horse serum and egg white is strikingly less intense than in adult rabbits immunized in the same way. He states that definite Arthus' phenomenon cannot be produced in young rabbits immunized with horse serum or egg white.

Psittacosis.—Two experiments designed to determine the nature of the causative agent of psittacosis were carried out by ARMSTRONG, MCCOY and BRANHAM (*U. S. Pub. Health Rep.*, 1930, **45**, 725). In each test this virus was found to pass through a filter (Berkefeld N). MCCOY (*Ibid.*, 843) reports 11 cases of accidental psittacosis infection among 54 persons employed in one of the units of the Hygiene Laboratory, Washington, D. C. Two of the infections were readily traceable to contact with infected birds, and a third case worked with cultures from infected birds and persons, but these are not considered the probable source of infection. In the remaining 8 cases there was no clue as to the source of infection, save that the victims worked in the building

in which infected birds were kept. There was no reason for considering the infection as transmissible from person to person. This is said to be the first example of infection not traceable to contact with infected birds. An outbreak of psittacosis in a department store is reported by BADGER (*Ibid.*, 1403). In November, 1929, 12 parrots were secured: 8 died in the store and 1 died after having been sold. Four cases of psittacosis were reported by physicians, but a careful canvass of the personnel of the store showed that there had been a total of about 25 cases. The following symptoms were reported: Rather sudden onset; chills; fever; malaise; severe headache, most frequently occipital; loss of appetite; coated tongue; constipation (occasionally diarrhea); unproductive cough; marked bronchitis with indefinite areas, suggesting pneumonia; fever reaching 103° or 104° F.; lack of definite gastro-intestinal symptoms; lung pathology out of proportion to other findings; delirium varying in degree; leukocyte count normal or below. From the manner in which the parrots were handled in the department store, there existed ample opportunity for infection by both direct and indirect contact. The birds were cared for by 4 of the employees, 3 of whom became ill. Other employees would frequently visit and handle the birds. It was probably not rare for customers to come in direct contact with the birds. The opportunity for infection through indirect contact was also great, especially since the parrots were kept on a perch outside of any cage during the day and on one occasion had escaped from their cage and were free about the floor. Four of the cases, on whom complete histories were obtained from their physicians, denied any direct contact, 12 admitted direct contact, and in 1, due to death, the mode of contact was undetermined.

Acute Rheumatism in Childhood and Its Sequelæ.—STERLING (*U. S. Pub. Health Rep.*, 1929, **44**, 1488) says that it is estimated that 75 per cent or more of children under ten years of age who suffer from rheumatism have heart involvement, and heart disease stands high among causes of death in children. Children examined under fourteen years of age have shown a heart disease incidence of from 0.7 per cent to 2 per cent. The infectious etiology of rheumatism is favorably considered. The following is given from the prophylactic point of view: The general American program for the prevention of acute rheumatism in children includes the avoidance of infection, especially of the upper respiratory tract, removal of all foci of infection, frequent examinations of all children, careful hygiene, avoidance of the possibility of contact infection, and education of the general public as to the possible seriousness of any rheumatic manifestations.

Is Immunity to Scarlet Fever a Factor in Puerperal Sepsis?—A very favorable puerperal morbidity rate (9.33 per cent) was observed by PARR (*J. Prev. Med.*, 1930, **4**, 105) in a study of more than 1000 deliveries in the hospital of the American University of Beirut, Syria, a region of high scarlet fever immunity. The question is raised as to the possibility of this favorable rate being due to a group immunity within the streptococcus group.

A New Meningococcus-like Organism (Neisseria flavescens n. sp.) from Epidemic Meningitis.—Branham (*U. S. Pub. Health Rep.*, 1930, **45**, 845) studied 155 strains of meningococci in a period of two years (1928–1929) and found that about 9 per cent could not be assigned to any of the recognized groups. Among 47 strains received from Chicago, Illinois, there were 14 that found a homogeneous group but did not accord with any of the previously described types. In addition to the serologic difference the 14 strains differed from classical meningococci in failure to ferment carbohydrates and in production of a golden-yellow pigment. Morphologically the organisms were indistinguishable from ordinary meningococci. The new organism is designated *Neisseria flavescens* n. sp.

Immunity to Poliomyelitis as Shown by the Neutralization Test.—Aycock and Kramer (*J. Prev. Med.*, 1930, **4**, 189) record observations concerning immunity to poliomyelitis as indicated by the neutralization of the virus by the blood serum of: individuals who had had an attack of the disease, monkeys which had passed through the experimental disease, monkeys immunized with the virus, normal monkeys, and normal individuals of different ages from urban and rural populations. These tests in normal individuals are in conformity with and extend previous observations to the effect that a widespread immunity to poliomyelitis exists among individuals not known to have had the disease. Additional evidence is afforded that this immunity originates in exposure to the virus and, from the extent to which it occurs and the order in which it develops, that the virus spreads by person-to-person contact. In a second paper (*Ibid.*, p. 201) the authors report that serums of 21 adults from Atlanta, Georgia, having no history of poliomyelitis, unquestionably neutralized poliomyelitis virus in 18 instances, and failed to neutralize it in 2 instances; the results with the other serum were not clear cut, but apparently this serum should be counted as having neutralizing power. These tests indicate that immunity to poliomyelitis is equally extensive in warmer and cooler climates, and therefore suggest that the extent of the distribution of the virus in warmer climates is equal to that in cooler climates.

PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF NOVEMBER 17, 1930

The Glomerular Elimination of Urea in the Frog's Kidney—a Quantitative Study.—A. M. Walker and K. A. Elsom (from the Laboratory of Pharmacology, University of Pennsylvania.) Glomerular urine and plasma were collected from frogs and the urea content of the two fluids determined and compared. As a result of 43 such comparisons it was

concluded that the urea content of the two fluids is identical. This is regarded as additional evidence that the glomerular process is filtration. It is believed that the glomerular elimination of urea thus demonstrated is sufficient to account for the entire urea excretion of the frog without interposing any additional tubular activity other than that of water reabsorption. In determining the urea content of glomerular urine, the sodium hypobromite method was so adapted to use in glass capillaries that amounts of urea nitrogen as small as 0.000,001 mg. could be quantitatively determined in amounts of fluid as small as 0.1 c.mm.

The State of Water in Blood Serum.—F. William Sunderman (from the Laboratory of Research Medicine, University of Pennsylvania.) Our meaning of the term "free" and "bound" water is the same as that used by Gortner and by Hill. Free water is capable of dissolving substances added to it with a normal depression of the freezing point, while in bound water the dissolving power is zero. Our method of measuring the state of water in the serum is similar to the method used by Newton and Gortner in their studies on plant juices. The depression of the freezing point is determined on serum alone and on the same serum to which known amounts of a nonelectrolyte, such as saccharose, have been added. By measuring the water content of the serum, and by determining the depression of the freezing point of saccharose in a solution of the same concentration in water, a theoretical freezing point lowering may be calculated. If the content of total water behaves as solvent, then the calculated freezing point depression is equal to the observed; however, if the water is bound, then the observed freezing point depression will be greater than the calculated. From studies of the freezing point of serum we conclude that within 2%, the limit of error of our measurements, the content of free water of serum is equal to the content of total water.

A Simple Method for Controlling the pH of Oxygenated Locke's Solutions with Some Preliminary Results on Excised Gastric Muscle.—J. Earl Thomas (from the Laboratory of Physiology, Jefferson Medical College.) The purpose of this study was to develop a simple means of preventing the loss of CO_2 and consequent pH changes that occur when oxygen or air is bubbled through Locke's solution. The ideal method is to mix CO_2 with the ventilating gas at a partial pressure equal to the CO_2 tension of the Locke's solution. It is evident that if the ventilating gas is first brought into equilibrium with a carbonate solution in which the CO_2 tension is equal to that of Locke's solution, and which will not alter its CO_2 tension as a result of the loss of this gas, it can then be used to ventilate a Locke's solution without altering its composition. Certain alkaline phosphate mixtures (Na_2HPO_4, K_2HPO_4, NaH_2PO_4) to which an excess of powdered magnesium carbonate has been added satisfy the requirements of the carbonate solution mentioned above.

The CO_2 tension of the phosphate-carbonate mixtures can be varied by altering the concentration of phosphate, consequently air bubbled through such mixtures can be used to maintain various CO_2 concentrations (or to vary the pH) in a Locke's solution. Mixtures have been

prepared which will serve to maintain any desired pH in a Locke's solution (0.015% $NaHCO_3$) between 6.0 and 8.3.

It has been found that the CO_2 tension of the phosphate-carbonate mixture, as indicated by the pH of the Locke's solution, varies with the concentration of total phosphate. Although a certain amount of acid phosphate is necessary for each mixture the amount that is used does not determine the ultimate CO_2 tension of the mixture. If too much is added the mixture loses CO_2 rapidly and at the same time becomes more alkaline until a certain constant tension is reached which is characteristic for each concentration.

The physicochemical reasons for the behavior of these mixtures have not been investigated. However, it is evident that the CO_2 is obtained from the decomposition of carbonate. Probably the alkaline products of decomposition of the carbonate are relatively insoluble in the phosphate solutions and therefore do not alter their reaction.

The most useful mixtures are the following: M/2 Na_2HPO_4, 400 cc.; M/2 NaH_2PO_4, 50 cc.; powdered magnesium carbonate, 25 gm. Air passed through such a mixture maintains a pH of 7.4 in Locke's at room temperature or about 7.6 at blood temperature. A mixture of the same concentration made with the corresponding potassium phosphates (20 cc. instead of 50 cc. of the monobasic salt) gives results about 0.1 pH more acid.

This method is being used to control the reaction of Locke's solutions in a study of the effects of changes of pH and of bicarbonate concentration on excised smooth muscle of the stomach. The results so far obtained indicate that increase in the concentration of bicarbonate up to 0.045% increases the rate of the rhythmic contractions of the stomach muscle. Higher concentrations do not cause a corresponding increase in rate but have no deleterious effects (up to 0.15%) if the pH is kept within physiological limits.

The Absorption of Sodium Chlorid from the Intact Gall Bladder.—G. S. Ravdin and C. G. Johnston (from the Laboratory of Surgical Research, University of Pennsylvania.) The manner in which the gall bladder empties itself is still disputed. Accumulating data tend to disprove the contention that its function is purely a passive one. The question most under discussion is whether the gall bladder absorbs everything that enters it, or whether the residue of the concentrated bile is evacuated into the duodenum by way of the cystic and common ducts. It seems probable that the answer lies in a study of the fate of the various constituents of the bile separately as well as in whole bile, in a gall bladder whose ductal connections are completely isolated from the liver, but whose lymphatics and bloodvessels have not been disturbed in any way.

The procedure, which we have made use of, has the advantages that we are able to study the action of the gall bladder on simple solutions or on known amounts of liver bile. We are able to observe changes in volume as well as in concentration, and to do this without traumatizing the gall bladder wall by repeated puncture, which Winkenwerder has shown permits of the more rapid loss of dye through the gall bladder wall.

We have studied the absorption of various concentrations of sodium chlorid in 22 animals upon whom 57 experiments were performed. The Wilson-Ball modification of the Van Slyke method for estimating chlorids was used.

Sodium chlorid was placed in the gall bladder in several concentrations. It was found that when a 0.4% solution of sodium chlorid is introduced into the gall bladder the concentration increases until the solution within the gall bladder reaches a concentration of chlorid similar to that found in blood serum. Sodium chlorid introduced at approximately the level of serum chlorid changes practically not at all. Water leaves the gall bladder steadily in either case.

When hypertonic solutions of sodium chlorid are introduced into the gall bladder (for example, 1.4% and 1.6%) water is drawn into the gall bladder. The concentration of the salt within the gall bladder decreases due to the actual loss of chlorid as well as to dilution. The volume of fluid within the gall bladder increases until the concentration of chlorid reaches approximately 1%. The volume of fluid in the gall bladder then decreases steadily.

If the gall bladder wall is injured by the repeated injection of hypertonic sodium chlorid solutions, a condition analogous to hydrops occurs. In such instances fluid pours into the gall bladder, and the chlorid concentration is approximately at blood-serum level.

When, however, a duct entering the normal gall bladder is not ligated and a small amount of bile mixes with the chlorid solution, the chlorid rapidly falls to as low as 0.2%. This agrees with the findings of Gamble and McIver, who found a lower chlorid content in gall bladder than in liver bile.

From this we are led to conclude that the behavior of the gall bladder wall to the passage of chlorid is very similar to that found by Goldschmidt and Dayton for the small intestine.

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